FOOD AND DRUG ADMINISTRATION

CENTER FOR TOBACCO PRODUCTS

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

(TPSAC)

Open Session

THURSDAY, FEBRUARY 10, 2011

1:15 p.m. to 5:30 p.m.

9200 Corporate Boulevard

Rockville, Maryland

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:14 p.m.)

Call to Order

DR. SAMET: Good afternoon. We are going to go ahead and get started with this meeting of the Tobacco Products Scientific Advisory Committee. I'm Jon Samet, chair of the Tobacco Products Scientific Advisory Committee. I want to make a few statements, and then we will introduce the committee.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine

Act, we ask that the advisory committee members take care that their conversations about the topics at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks.

I'll just make a note. If you look through the schedule carefully, you saw that there was no break included. But I think before the open public hearing, we'll take a brief break.

Caryn?

Conflict of Interest Statement

MS. COHEN: The Food and Drug Administration is convening today's meeting of the Tobacco Products Scientific Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and non-voting members

are special government employees, or regular federal employees from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 U.S.C., Section 208 and Section 712 of the federal Food, Drug, and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and federal employees who have potential financial conflicts of interest, when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress

has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary, to afford the committee essential expertise.

Related to the discussion of today's meeting, members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves receiving an update on the menthol report subcommittee and receiving and discussing presentations regarding the data requested by the committee on the March 30-31, 2010 meeting of the Tobacco Products Scientific Advisory committee.

This is a particular matters meeting during

which general issues will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all committee members to disclose any public statements that they have made concerning the issue before the committee. With respect to FDA's invited industry representatives, we would like to disclose that Drs. Daniel Heck, and John Lauterbach, and Mr. Arnold Hamm are participating in the meeting as non-voting industry representatives, acting on behalf of the interests of the tobacco manufacturing industry, the small business tobacco manufacturing industry, and tobacco growers, respectively.

Their role at this meeting is to represent these industries in general and not any particular company. Dr. Heck is employed by Lorillard Tobacco Company. Dr. Lauterbach is employed by Lauterbach and Associates, LLC, and Mr. Hamm is retired. FDA

encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

I would just like to remind everyone present to please turn off your cell phones so that we don't get feedback with these microphones. And I would also like to identify FDA's press contacts, Jeffrey Ventura and Tesfa Alexander. If you're here, please stand up. Thank you.

Introduction of Committee Members

DR. SAMET: Then let me begin with committee introductions, I think starting to my right. Neal?

DR. BENOWITZ: Neal Benowitz, University of California, San Francisco.

DR. DELEEUW: Karen DeLeeuw, Colorado Department of Public Health and Environment.

DR. HATSUKAMI: Dorothy Hatsukami, University of Minnesota.

DR. HENDERSON: Patricia Nez Henderson, Black Hills Center for American Indian Health.

DR. HENNINGFIELD: I'm Jack Henningfield, Pinney Associates and the Johns Hopkins School of

Medicine.

DR. CLANTON: Mark Clanton, representing pediatrics, public health, and oncology.

DR. DEYTON: Lawrence Deyton, Center for Tobacco Products.

DR. ASHLEY: David Ashley, Center for Tobacco Products.

DR. HUSTEN: Corinne Husten, Center for Tobacco Products.

DR. KAROL: Susan Karol, Indian Health Service.

DR. CLARK: Westley Clark, Substance Abuse and Mental Health Services Administration.

DR. BACKINGER: Cathy Backinger from the National Cancer Institute, representing the National Institutes of Health.

DR. LAUTERBACH: John Lauterbach, Lauterbach and Associates, representing the interests of the small business tobacco manufacturers.

DR. HECK: Dan Heck with the Lorillard Tobacco Company, representing the tobacco manufacturers.

MR. HAMM: Arnold Hamm, representing U.S. tobacco growers.

DR. SAMET: I think we have Tim on the phone.

DR. MCAFEE: Hi. This is Tim McAfee, representing the Center for Disease Control and experimenting with modern communications technology to participate.

DR. SAMET: So far, so good.

DR. MCAFEE: Great. Thanks.

DR. SAMET: I think, as our first item, we'll turn to Corinne for a presentation on the menthol report.

FDA Presentation – Menthol Report

DR. HUSTEN: As a reminder, the charge to the Tobacco Products Scientific Advisory Committee is to produce a report and recommendations on the impact of the use of menthol in cigarettes on public health, including such use among children, African-Americans, Hispanics, and other racial and ethnic minorities, and the report is due March 23rd of this year.

I will briefly go over what to expect, because I think as the committee's been progressing, there have been questions about how this is all going to work. So we have a meeting tomorrow of the Menthol Report Subcommittee. We have a full committee meeting scheduled for March 1st and 2nd, and a full committee meeting scheduled for March 17th and 18th if needed.

Draft chapters of the report will be discussed in open public meetings of the TPSAC as they become available. FDA intends to make chapter drafts available to the public as background materials on the FDA website at least two business days before meetings where the draft chapters will be discussed. The availability of draft chapters as background materials is contingent on the committee's progress. Thus, we can't specify at which upcoming meetings draft chapters will be available as background materials.

The final report will be made available to the public on FDA's website once it's been reviewed for redaction of any commercial, confidential, or

trade secret information. Once the report is received, FDA will consider the report and recommendations of the committee, as well as other scientific evidence concerning menthol cigarettes and make a determination what actions, if any, are warranted. There's no required deadline or timeline for FDA to make such determination. Any sale, distribution restrictions, or product standards are implemented with notice and comment rulemaking.

I wanted to give a brief summary of the status of the information requests that had been made by the committee. One of the first requests was to obtain the peer-reviewed literature on the topic of menthol cigarettes, and we got input from our committee members, from the public, from our industry representatives, and all that has been provided to the committee.

At our second meeting, there were a series of industry presentations. There was a Legacy database document review that was presented at an earlier meeting. The committee had recommended

some secondary data analyses from existing data sources, and those were completed and presented. There was a review of marketing data, including both Nielsen and Federal Trade Commission data analyses.

There was an industry document request, and those analyses have been completed except for Topics 5, 6, and 7, which are in progress. And a model on the effect of menthol on initiation and cessation was requested, and that model is also in progress.

We do expect that that February meeting is the last meeting where FDA intends to provide new information to the TPSAC, except for the completion of the model on the effect of menthol cigarettes on initiation and cessation, or to provide any information specifically requested by the committee in terms of clarifying information previously presented.

Analyses of industry documents submitted in response to Topics 5, 6, and 7 are not expected to be completed in time for consideration by TPSAC in

preparing the report. Those analyses are underway, and they will continue, and they will be considered by FDA once they're complete.

Today's meeting initially, this morning, was a closed meeting where commercial, confidential, trade secret information from industry document submissions and confidential FTC data were presented.

We're now having the open meeting, and information from industry document submissions on Topics 1, 2, 9, and 11, and 12, that can be shared publicly, will be presented. There will be an update on the model of the impact of menthol on initiation and cessation. There were a few questions that were posed to RTI at the last meeting, and there'll be two brief presentations with those clarifying analyses. There will be the open public hearing for public comment and then a discussion of chapters one and two.

Again, analyses of the documents identified by the industry as responsive to Topics 1, 2, 9, and 11, and 12 have been reviewed by RTI under our

contract. And the RTI review -- or our review of their summaries has determined that some of the information is commercial, confidential, trade secret. That information was provided to the TPSAC SGEs. But the information that was not deemed commercial, confidential, or trade secret will be presented at today's open meeting; however, that data, in some cases, is very limited.

So the questions we have for the committee today are what comments does TPSAC have regarding the proposed model, and what feedback does TPSAC have regarding draft chapters 1 and 2?

Are there any clarifying questions?

[No response.]

DR. SAMET: Thank you, Corinne. Then we'll move onto the presentation by Dr. David Mendez from the University of Michigan School of Public Health. We, of course, heard from David in our last meeting with regard to the development of a model that would provide us with input with regard to our charge, assessing the public health impact of menthol in cigarettes.

This is still a work in progress, and David will be presenting, describing the progress that he has made, I think also, to continue to have a dialogue with the Menthol Subcommittee and TPSAC, concerning the identification of model parameters. And, again, as you know, we intend to link our reviews of the literature in support of whatever parameters are provided to him, along with ranges for those parameters for the modeling purposes.

Today, what you're going to have is an opportunity to revisit the model, and also to get a sense of the kinds of output that the model can potentially provide. The scenarios that David is going to tell us about are completely hypothetical, and theoretical at this point, and are not grounded in discussions with the Menthol Subcommittee, but are intended for purposes of illustration, and I think in part, to orient the Menthol Subcommittee to what can be forthcoming from the model.

So if you see a number there, that is solely for purposes of illustration. So thank you, David.

Model Presentation – David Mendez

DR. MENDEZ: Thank you very much. I'm David Mendez from the University of Michigan. I'm building a model to track menthol cigarette smoking. And let me reiterate this again, that the constructs of the model are still preliminary. So the model is built as it stands right now, but I still have to test the construct of the model and receive more feedback from the committee. Also, I put some data for testing the model, at least just to check the kind of inputs and outputs that we need. And all the numbers that the model I am producing are totally hypothetical, so they are not grounded in any kind of real data.

So let me recap the construct of the model. The very basic model, the very basic idea, is that we are building a compartmental model that tracks prevalence, and compartmental model is just to keep track of a bucket of elements. And those buckets are smokers, and those smokers are differentiated by different characteristics. They are former smokers, current smokers, with different ages. And what we are keeping track of is what is in that

bathtub, and it's regulated, that volume, by the rate of initiation and cessation.

So that's the very basic construct, but inside the model, then, we are separated, those elements of compartments, into never smokers, former, and current smokers. And, ideally, what we can do is compare different scenarios and figure out what the difference is. If we have a different scenario for initiation and cessation, we can compare, at the end, the different characteristics and the outputs of the model.

So, of course, all these characteristics of the model are driven by mortality rates, and relative rates for former and current smokers, by age and years quit, that were estimated from CPS, Cancer Prevention Study II data.

So let me recap. This is the model that I presented and implemented from the presentation that we had last time. The model was implemented, and the green circles are the data that we already have, and the red circles are the data that we were requesting from the committee to inform the model.

Initially, we have an initiation, so the blue boxes are the compartments. And inside the compartments, we are differentiating those compartments by every year of age from zero to 100.

What we have in the model, the construct, the initial construct of the model, is that we have a birth rate that creates a volume of children less than 18 years old, and, at that point, there's an initiation. At the request of the committee, in the current version of the model, we have the initiation age varying, so we can model different populations that have different rates, initiation ages.

So once a person with certain rates become a smoker or remains a non-smoker, then at the same time, there are rates of separation in that initiation between menthol and non-menthol smokers. So we have a rate of menthol initiation, a rate of non-menthol initiation, and then a flow of individuals that are never smokers.

Then after that, they become current smokers, and they age, and they can leave those

compartments, by death, by quitting, or by transitioning to either menthol if they are a menthol smoker or non-menthol if they are non-menthol smokers. If they quit, they go into the former smokers categories. And in this case, by a modeling choice, I am not making a difference between former smokers that come from menthol or non-menthol.

So they are former smokers, and then they follow from there, a trajectory of declining in the relative risk, depending on their age and age quit. Then they, of course, can leave the compartment by death. And former smokers -- by the way, I'm considering permanent quits in those buckets. And, at the very end, we have the death compartment, and keep track of, if we have different scenarios, differential death.

So the specific parameters to that, I'm requesting from the committee, are going to be much more clear in the last stage of the presentation. But for now, let me give you an example of the data that the model can produce. And I can produce,

because the model keeps track of every single year of age, how many people are in the different categories, and we can produce other sets of outputs at the request of the committee.

So, for example, I am comparing in this case, a scenario which is what we call Scenario A to Scenario B. In Scenario A, we are assuming that age 18 is the initiation age. And then the overall initiation age in this case is 21 percent, so 21 percent of 18-year-olds become smokers.

There's a proportion of menthol initiation, which is about 47 percent in this case. That means given a menthol initiation rate of 10 percent and a non-menthol initiation rate of 11 percent in this case, which gives me a ratio of menthol to non-menthol initiation of .89. Then we have cessation rates that are over all cessation rates. And the model, given the prevalence of menthol or non-menthols, then separates the right rates of -- cessation rates for non-menthol or menthol.

But in this case, the overall cessation rates were estimated some years ago for another

project, and they're about 2.6 percent per year, in general, and separated by age, discriminated by age. Then I have a parameter that is the cessation rate of menthol to non-menthol, the ratio. So, in this case, I am assuming, in this Scenario A, that menthol smokers have 25 percent less cessation than non-menthol smokers. Then I have a probability of switching from menthol to non-menthol, but I put them at the same, so they will cancel out in this case. I just didn't want to have any sensitivity to that.

Then if you see the results, then I keep track of those results. When it says Scenario A -- on the right part of the slides, it says Scenario A, menthol prevalence, and non-menthol prevalence, and overall prevalence. So keep track of the prevalence of menthol and non-menthol for up to year 2010 to year 2050.

For Scenario B, what I have under Scenario B is a situation in which we have no menthol at all, and the overall initiation rate is 18 percent instead of 21 percent. So give me the proportion

of menthol to non-menthol, the proportion of menthol initiation of zero, the non-menthol initiation rate is of course 18 percent if everything is non-menthol. And the probability of switching to a non-menthol, I just put 1. It's just an artifact of the model, so we can just switch all the -- I just wanted to make sure that the model is behaving with those probabilities correctly and put everything into the non-menthol category. But that is not really relevant in this case.

But when you see the Scenario B, it talks about no prevalence of menthol, the non-menthol prevalence slows down from 20.5 to 10.5 percent, and at the very end, when we compare those two survival curves year by year, and keep track of the number of deaths, that's the cumulative differential deaths between the two scenarios, starting in 2010, really after 2010 and start adding those differential deaths.

So that's, again, one totally hypothetical scenario. I just wanted to figure out whether the

model is -- I just want to put numbers to see whether the model is at least behaving at least in the right direction.

The next slide is pretty much the same. It's another hypothetical example in which now you have the menthol initiation rate at about 9 percent, and the non-menthol initiation rate is 12 percent. So the proportion of menthol initiation is slower than in the first one, just to do some sensitivity analyses from that.

The cessation of menthol to non-menthol is a little bit more similar. It's more similar in the previous case. So there's a 10 percent lower cessation for menthol than in non-menthol. And pretty much the same scenario going, everything to 18 percent initiation, and you can see the different scenarios, how the prevalence in both Scenario A and Scenario B is declining, and the difference in prevalence under both scenarios and the difference in mortality.

One of the things that we can produce very easily is also a (unclear) years saved that I just

didn't put here, but if the committee requires that, it's a really easy output to have.

So the constructs of the model are the model is built, and going to different populations is an idea of changing the parameters of the model of this point. So the basic constructs are -- the stage that I'm at is I need a little bit more time to actually test the constructs of the model to make sure that the equations that I have on paper match exactly what is happening inside all the computations and the programming of the model. So there are going to be some tests of the validity of the model to make sure that what I want to represent is actually happening. Everything is behaving in the right direction, but it needs a much more careful testing in this case, just to make sure that everything is fine.

Then, the request to the committee is the parameters. Okay? So that's the part that I need your input on. And I made a table with the most specific parameters that I need, and kind of the ranges that I need. So instead of one single

parameter, I would like a range from minimum to maximum. So if I could have the initiation ratio from menthol to non-menthol, minimum/maximum of the most likely parameters -- the cessation ratio, menthol to non-menthol, the mortality rate, if you think there's a mortality ratio, menthol to non-menthol. There's a way to input that into the model; switching rate to menthol, to non-menthol.

If you think that can be discriminated by age, there's an easy way to put that into the model. So it will act with one single parameter, one single data point. But if you think that the switching changes with age data, that people in their 40s or 50s are less likely to switch than people in their 20s, then that can be very easily integrated in the model.

But the mean, the maximum, and the most likely will allow me to present a full range of sensitivity values, but at the end, also, I would like to conduct a full Monte Carlo simulation on those. So what if all these parameters act with a range of uncertainty at the same time; what is the

range of uncertainty that we have in the output? So we can see not just the parameter by parameter, what sensitivity, but also for what we know, what we can say, in what range.

So this is where we are, and I would welcome comments and questions.

DR. SAMET: Thank you, David, and I know you've been working very hard. And I think these next 45 minutes are, I think, very important for us to be aligned with David.

I'm just going to try and guide us through the discussion, perhaps, and maybe if we went back first to the black diagram, your basic description of the model, and maybe just start there and see. I think we had a little bit of a dialogue about this last time; do we see the model as, in a sense, representing these relationships the way they will be portrayed in our report. In our chapters 1 and 2, we have already set out I think a very similar sort of compartmental model.

But I think we should pause here, and I just want to remind everybody, last time, we did discuss

the need to have ethnic racial groups, specific models. And this is something that David can do, and, of course, it involves modeling different populations, different population structures, and so on.

So David guided us through this, but let's stare at it for a while and just see if anyone has questions or comments. Remember, this is how we're portraying the way these relationships are or our best representation of them. So let's see if there are comments here.

Yes, Mark?

DR. CLANTON: At some point, our charge is to look at comparing menthol, say menthol death rates to death rates of non-menthol cigarettes. So help me understand. It looks like we have a single output of the model, which is death, which is a combination both of death from those who smoke non-menthol cigarettes versus those who smoke menthol cigarettes. So help me understand how we get a comparative analysis of those two subgroups versus a single output of death for the combination.

DR. SAMET: Actually, before you do that, let me just interject. This is where the interaction would be with chapter 6, which Neal and I are working on, where we are assessing a whole spectrum of evidence relevant to the question, in the end, of whether the relative risk for mortality for the various diseases caused by smoking are the same or different.

So we would be supplying David with a range, and that was, I think, the last parameter in his table, in fact, for these comparative relative risks for menthol versus non-menthol smokers.

DR. MENDEZ: Yes.

DR. CLANTON: Let me just sort of elaborate a little bit. It looks like you're looking at a population risk of death due to smoking, which happens to be the sum of both non- and menthol cigarettes.

DR. MENDEZ: But in the compartments, I have the compartments of smokers that smoke menthol and the compartments that don't smoke menthol. And I have the death rate of each one of them. So I put

them together, but I can keep them separately.

DR. CLANTON: Okay. Actually, that answers my question.

DR. SAMET: Actually, Mark, one way that the model would be useful is, let's say for the sake of argument that a range of comparative relative risks is given. I'll make up a number because it's totally hypothetical. It goes from 0.5 to 1.5 for the comparative risk of death from lung cancer, et cetera, in smokers versus non-smokers. So David could simply run a range without varying any other parameter in the model, and then you would have the predicted numbers of deaths in the total population under different values of comparative risks.

So let's say that you have a number at the bottom of, I don't know, 30,000 if the value is 1 and 22,000 if it is 0.5, and there we can then look exactly at what's happening.

DR. MENDEZ: The model is prepared right now to compare two different scenarios at the same time. So just put two different scenarios and actually keep track of the whole thing, and it

tells you, this is the difference between the two.

DR. SAMET: Dorothy?

DR. HATSUKAMI: David, my question is, what if you don't have a lot of data to fill in some of these? Like, for example, the initiation ratio, what do you do in that particular situation?

DR. MENDEZ: Well, the idea is we need to have the best estimate that we can have. Even if we have a range of estimates between -- for example, the probability of initiation of menthol or non-menthol, the question is then to run the model by each one of those parameters and see which one it's more sensitive to. It might be that the parameters that don't have enough data might not make too much of a difference. Right? But if it does, then we actually need to zero in on that and then produce the best possible estimate.

DR. SAMET: Actually, Dorothy, I would have reframed the question to not what will David do, but what will we do. In fact, it's going to be our job to review the literature. And, certainly, there'll be varying degrees of certainty around the

parameters that we give to David, and that uncertainty could be expressed in terms of the range that we give him, or, depending on how sophisticated we have it, in terms of building it under varying distributions and the Monte Carlo work you do. And I think we'll have to see where that goes.

Patricia?

DR. MENDEZ: Right now, we have a very basic triangular distribution built for the most likely minimum and maximum, and it will give pretty much a nice range of variability there.

DR. HENDERSON: What about other social factors, social economic factors like education? Can you throw that into the model as well, or different communities?

DR. MENDEZ: I could, depending on how soon you wanted it. I could.

DR. SAMET: Corinne?

DR. HUSTEN: I'm sorry to be off topic here, but if everybody could please check, and if you have any cell phones that aren't turned off or

anything that uses phone technologies like plug-in phone cards for your computer, anything that's related to using phones is going to create interference, and our poor transcriptionist is bearing the brunt of it. So if you'd please check, if you have more than one phone, make sure they're all off, and if you're using a phone card, please stop.

DR. SAMET: And you might as well turn it off because it doesn't work here anyway, which is why we're here.

DR. HUSTEN: That's why it has to be turned off, though, because it's continually searching, and that's what creates the interference.

DR. SAMET: Mark?

DR. HECK: Yes. Dr. Mendez, as I think Dorothy alluded to, populating this model with some meaningful numbers, that's really the difficult part. We do have, for some of these parameters, perhaps, a natural experiment that I'm wondering might be useful to test the validity or to firm up the model. And that is, we have countries around

the world, for instance, where the menthol is essentially unknown on the marketplace. And we have WHO and smoking data, mortality data, that kind of thing.

Do you think that those sorts of data could be used to test this model, validate this model?

DR. MENDEZ: I need to check the data to see.

DR. SAMET: Mark?

DR. CLANTON: This is more of a question about how the committee wants to use this model. So, clearly, you have an interest in terms of as you referee the evidence in chapter 6, this model is going to be helpful. But also, it's going to be enormously helpful in chapter 7 under the section on public health impact or comparable public health impacts.

So are we going to end up arm wrestling over who gets to use the model, or is that going to be used across different parts of the report?

DR. SAMET: So I guess the answer will turn out to be what it turns out to be, but I do think

that you're right in terms of –

DR. CLANTON: Utility.

DR. SAMET: -- utility, that this is really I think an integrative tool, that we want to look at the output of the model in relationship to the various indicators that we have said are relevant to our charge.

So I think probably the results will figure most prominently in chapter 7, Mark, I think which is your suggestion.

Other questions about the workings of the model itself, the arrows? And, again, they're embedded assumptions, as David pointed out. For example, former smokers of both menthol and non-menthol cigarettes are in the same compartment, which seems reasonable. But if anyone's been looking at those arrows sees things that they think are not the way the world might actually work, this is a good time to provide that input.

Yes, Neal?

DR. BENOWITZ: I don't think we will have the data, but one issue is, really, the time at

which quit attempts occur for menthol versus non-menthol. So, for example, some studies suggest that it takes menthol smokers longer to quit. They may quit eventually, but they relapse more, so it takes them longer. It looks like your model assumes that they're the same quit rates at different ages, at a different proportion.

DR. MENDEZ: No. Oh, yes, exactly. So you are right. There are different quit rates at different ages. Right now, I have in the model very little in general, very little cessation in the 20s, then more cessation in the 30s, more cessation in the 50s. So the way they model works right now is adjusting that proportion, that overall curve as to menthol and non-menthol.

Now, it could be, then -- so assuming the same pattern of quitting for menthol or non-menthol right now. So it might be that the menthol smokers take much longer to quit, but in this case -- they take much longer to quit, but much longer also, in relative ages, the older people with menthol are taking much longer to quit, too. So I'm not

changing that pattern.

DR. BENOWITZ: Right. And I don't think we'll have the data, but that certainly is a potential shortcoming because there are theories that menthol might work by delaying quitting rather than preventing quitting. And then we wouldn't pick that up in this model approach. But we won't have the data to provide to you, but that would be a limitation of --

DR. MENDEZ: But why wouldn't that be the same? If your quit rate per year is lower, the person is delaying quitting.

DR. BENOWITZ: Well, an issue would be, say by age 55, the same numbers quit in both groups, but it just takes longer for the menthol people to quit, then this assumption in this model wouldn't be right, and you would miss some impact on disease. I'm not sure what to do about that.

The other thing, which is something that I've been interested in, which this model doesn't pick up, if you look at deaths, you miss a lot of morbidity that's important, including infections,

including a lot of things that occur in younger smokers. So you might quit smoking by age 50 and avoid a lot of the death consequence, but still have a lot of morbidity.

DR. MENDEZ: Correct.

DR. BENOWITZ: And I guess the model just won't be sensitive to that.

DR. SAMET: Mark?

DR. CLANTON: Neal, I think there may be one way of dealing with that. You can also use costs of healthcare by age group, or at least by specific chronic diseases as a proxy for morbidity. And so certainly Medicare databases, there is that kind of information. There may also be published data on costs of care by cardiovascular disease, cancer, et cetera, for other age groups as well. So we might be able to get a proxy for morbidity without trying to go directly to that.

DR. MENDEZ: I just want to, for my own clarification, just get back to your point of cessation so I can understand it.

DR. SAMET: I think, actually, what he's

suggesting is that there are age-type interactions in the comparative rate of cessation. And by assuming constancy in age, you may not be capturing what Neal is hypothesizing could be different time courses of cessation by age, perhaps, even patterned such that by some age, whether it's 55 or 60, the actual proportion of quitters is the same in the two groups, but they got there by different trajectories over aging.

I suspect in the infant mortality, those kinds of subtleties might not make much of a difference. I think if as we review the literature, we find strong evidence that such might be the case, then I think we could talk about pursuing it.

Just as a comment on indicators other than mortality, I'm sure we're not going to get any work done on those in the next few weeks. But, again, I think in terms of building generally useful tools for the future, those kinds of considerations I think are quite important.

Let's see. Other caveats? I have a few

more questions myself. We're just still on the boxes, the model itself. So why don't we open up for broader discussion? And I think, again, just to have clarity – actually, David, I have a question on the -- I was thinking about the initiation parameter. And as I was thinking about it -- and I'm not sure whether it's captured or not.

There are two aspects of the type in initiation that could be important. One is the proportion of initiators or experimenter initiators using menthol versus non-menthol. The other is the relative rate of progression from initiation or non-smoker to smoker by type. So it seems -- does your parameter -- I'm not sure it captures both of those.

DR. MENDEZ: No. It doesn't. You are supposed to have an overall number like that. So when we deal with age of initiation, it is what is going to be the permanent non-smoker, the permanent menthol smoker, permanent non-menthol smoker, and non-menthol? So, essentially, all the fluctuation

that happens at early ages are not captured here.

DR. SAMET: Let me ask, do we need on the left-hand side never smokers who are going to initiate? We have initiators with menthol, initiators with non-menthol, non-menthol initiators to current smoker, non-menthol initiators to current smoker. And then we have two things we need to provide to you. One is the split between menthol and non-menthol initiation, and the other is, at least, a comparative rate of moving from menthol initiation to current smoker and non-menthol initiation to current smoker.

DR. MENDEZ: Yes. But then I can combine that into one parameter, which is this. See, my point is, do we need the compartment to keep track if that's not going to make too much of a different in the model? I mean, there's almost no mortality at early ages. So the question is, that interaction can be just so highly likely with one parameter.

DR. SAMET: I think I've got it. So maybe just to make sure I'm not being dense, which I

might be. Take us to your comparative initiation ratio, and let's make sure we've what it is.

DR. MENDEZ: So let's say that this is the prevalence at 18 to 24 years old, right now, is 21 percent. So that's what I'm taking to be the initiation rate for it, so 21 percent of 18-year-olds of current smokers. Out of that proportion, what proportion is menthol and what proportion is non-menthol? That's what it is.

DR. SAMET: That's assuming my other --

DR. MENDEZ: Exactly.

DR. BENOWITZ: If you try to break down the elements of what influences these things, though, it could differ. For example, suppose you try to separate out advertising effects, which might affect whether a never smoker tries a menthol cigarette, versus pharmacologic addiction, which is once you try it, you become addicted, so it could have different effects on different parts of that equation.

DR. MENDEZ: That's a very good point. That, we can separate if --

DR. SAMET: Let me ask, sort of looking over at Dorothy, to see if -- in terms of the utility of the model or the strength in the utility of the model for our purposes. I think what I commented, then I think what Neal reinforced, is whether we want to uncombine these two steps in the process that David has combined into one in the model.

So one would be factors influencing the choice of cigarette with which experimentation initiation goes on, menthol, non-menthol. The other is the comparative rate of progression from experimentation, initiation, to current smoking, which as Neal points to, might be dependent on other factors. And then thinking about the kinds of outputs that might come from your group, I think it might be useful to separate these.

DR. MENDEZ: It depends on what you want to do with the model; if you want to analyze different potential interventions.

DR. SAMET: Actually, I think from the point of view our thinking, the way we've divided our task, and thinking about those factors that lead to

initiation, to menthol or non-menthol, and then questions as to whether one type or another has a greater liability to produce -- to lead to an addicted smoker, it might be useful to extend the model to the left.

DR. HATSUKAMI: I am in total agreement with that.

DR. SAMET: Jack?

DR. HENNINGFIELD: It's such a balancing act, trying not to make the model so complicated that it's useless, but I think the idea of a range of parameters is useful. And if we start with something like the 2010 surgeon general's report figures on approximately 4,000 young people trying smoking every day, which adds up to 1.4 million or something per year, about a quarter of those making the transition to daily smokers every day; then the question is, if we assume we can look at population data on what fraction are menthol smokers --

But I think part of where Neal was going to, and part of the challenge is, if menthol increases the risk of transition from experimentation to

daily smoking, then it's having a more complicated effect. And I don't think there's any way to say this is exactly what the number is, but I think we can come up with -- if we start out with the parameters that are in the 2010 SG and look at population data on youth menthol use, then I think we have a basis for saying, here's the current numbers. We have to factor in the possibility that if you took menthol out of the equation, there are a couple of effects and what is the upper range. Maybe that's the best we can do.

DR. SAMET: I think this has been a useful discussion, of course creating another line in the tangle that David is going to want us to complete. But I think it's a line we need to fill in, and we'll look for ways to do it.

Yes, Cathy?

DR. BACKINGER: I had a different question. Is it okay to move on?

So my question was -- and I know, David, you mentioned that these were just hypothetical data, but in the data needed to complete the model, I

didn't see over time what the overall estimate for prevalence would be. And I saw that in the hypothetical data, that you show that overall prevalence decreases from 2010 to 2020, all the way out to 2050.

So just to get a sense from the rest of the committee, we've had a flattened prevalence rate for several years now, so I'm wondering how you're going to determine what the overall prevalence would be out to 2050.

DR. MENDEZ: That's an output of the model and that depends on the cessation rates right now.

DR. BACKINGER: I'm sorry. So you're making the assumption that the initiation rate is constant.

DR. MENDEZ: The cessation rate is constant. We can actually change the initiation rate. Right now, here, the initiation rate is constant and the cessation rate also is constant, but that's something that can be changed in the model. But with a constant initiation rate, a constant cessation rate, we are predicting a decline in

prevalence. It's a bathtub.

DR. BACKINGER: Right.

DR. HENDERSON: Is that impacted by policies, like for example, in home policies on smoking and exposure to secondhand smoke, all these other factors?

DR. MENDEZ: You mean if initiation and cessation are going to be impacted?

DR. HENDERSON: Because it's so linear now that I guess I have a problem with it, with the model.

DR. MENDEZ: Linear what?

DR. HENDERSON: For me, I guess the factors that are very important are environmental factors, and the things that are happening down at the social level, all I see is just death, initiation. So all these other things that are very important are not a part of this model.

DR. SAMET: They are, because they are the drivers of these parameters. And I think what we're getting at in this discussion is that, at the moment, the model is rather static in time on some

of these parameters. If we think that there's a reason to have one set of cessation rates, let's say for the different intervals, that could potentially be built into it as David projects forth.

If we feel that, with some certainty, we could predict the future and suggest that cessation rates might rise, for example, those kinds of scenarios could be built in. I think what I want to make sure we have is a useful tool and one that reasonably represents things, and then we will have to interpret it within the uncertainties. And, clearly, as we go out further and further in time, the uncertainties mount. And I think we'll have to think as a committee about what our horizons are as we give varying degrees of credibility to interpreting the model findings.

Again, this may be something that we want to propose, that from 2010 to 2015, let's keep the world as it is, but from 2015 to 2020, perhaps we augment the cessation rate by X, and that could be done.

I just want to see -- Tim, did you want to say something?

DR. MCAFEE: I just had a quick comment that is kind of along the same lines, but looking at one specific issue, and that's essentially whether this model would -- if rather than assuming static rates of -- I'm much concerned of a long sweep of time around this, but really that there's -- I think one of the likely scenarios is that there would be a very dramatic sort of unstable period over the first couple of years if there were a menthol ban, and that you would see a dramatic change in the people that were menthol smokers, as some of them decided -- if they were to make incremental decisions as to whether they switch to non-menthol cigarettes, or whether they quit completely, or whatever.

I guess my question's whether you think this model could accommodate to focus on that disruptive moment, that kind of first path effect that would happen during a very dramatic transition period. And, to me, that's a big question. There's this

other question that I think the model clearly is answering, which is more related to the stable, steady state scenario.

DR. SAMET: This is Jon. I'm going to step in and give the first answer here. The purpose of the model, I think from the perspective of the Menthol Subcommittee, is to have a tool to identify tasks estimating public health impact. And there the comparisons are sort of intrinsic to looking at sort of counterfactuals of not having cigarettes available with menthol -- having menthol brands available.

I think what you are speaking to is, in a way, something that might be at issue if, depending on what decisions are made and policy steps are taken to look at, sort of shorter-term consequences of perhaps moving from where we are now to varying policy scenarios that might be enacted up to having no cigarettes with menthol.

I think you're probably correct that the time dynamics that we are building under this model may be entirely inappropriate for such scenarios.

But I don't think those are tools that are going to be built immediately, nor do we necessarily need for our job of estimating public health impact.

But Corinne, I think you were going to weigh in, too?

DR. HUSTEN: Yes, I think trying to make the same point, that what we had asked Dr. Mendez to do was to model the public health implications of menthol cigarettes, not to model a ban on menthol cigarettes, where there's a whole other set of parameters that would have to be included.

So this is really more a modeling of the status quo versus a counterfactual situation of no menthol, because, as we all know, because of the issues brought up, to model a ban, you'd have to include a lot of other parameters, like do you think there's going to be counterfeiting, and smuggling, and changes in switching and stuff.

So this is based on what we know about menthol smoking and non-menthol smoking, and the counterfactual situations. So I just think that's an important point, though, that that's not what

this model is designed to do.

DR. SAMET: Dan?

DR. HECK: I apologize. My question is lagging a little bit, Dr. Mendez, but something Jack Henningfield said earlier got me thinking. You're fixing the initiation age in the model at 18 here. It does provide a certain amount of clarity. Not to minimize the youthful experimentation that leads to ultimate career smoking.

But Jack mentioned many studies, including the surgeon general's report, over the years have pointed out to us that about 75 percent of youthful experimenters don't go on to become lifetime smokers. So it's lifetime smokers that we are trying to get at here. Those are the real initiators we're worried about, not the experimenters.

I don't think it's useful for us to think of youth, let's say 12 to 17 or whatever, achieving 75 percent cessation. They basically never start or become smokers beyond just maybe whatever this youthful experimentation period is.

So I think there's a certain advantage, arbitrarily perhaps, to fixing the age to something like 18 where persons do make buying decisions. They go out and purchase those cigarettes. They are smokers, as opposed to the youthful experimenters, who apparently number about three out of four.

DR. MENDEZ: Yes. So that's one of the reasons, in the previous model that I built, I fixed the age at 18 just to avoid the confusion that happened before and then follow tracks.

Another quick comment about the linearity of the models; the prevalence has proven to be quite a linear process for a long time. I've been looking at this and feeding models with the data from the '80s, and I predict per year, with that data, pretty well what's happening right now with basic linear models, with very small changes in cessation rates. What we have seen are the drops in initiation rates that we can do with a sensitivity analysis, but the basic patterns have been pretty predictable in terms of the prevalence.

DR. SAMET: Corinne?

DR. HUSTEN: My only caveat to that was because of the later initiation among African-American smokers, 18, again, may not be the right age if you're going to go with sort of an overall age, because a lot of that transition from experimentation to more regular use occurs after age 18, but still within the next few years. But you may lose some initiators, true initiators, with a cut-off of 18.

DR. SAMET: Jack?

DR. HENNINGFIELD: Again, the balancing act is not overly complicating the model. I think we can't completely leave out the initiators who do not convert for two reasons. One, the law says effects on initiation must be considered, and two is the possibility that menthol affects the conversion rate from initiation to daily use.

So would the conversion rate be lower if menthol was not in the equation? And I think, given the fact that we don't know for certain, but we've been presented with evidence that suggests

that it increases the conversion rate, I think the model has to anticipate a world in which menthol is or isn't there, and how that would affect conversion rate. So I think, for those reasons, we can't leave it out.

DR. SAMET: I think we've put it in, in fact.

Neal?

DR. BENOWITZ: On another caveat related to age, I think there is one study somewhere that suggests that if you look at really young smokers, like 13, there is a bigger differential of menthol versus non-menthol. And we know that the earlier kids start smoking, the more likely they are to become an addicted smoker. And so people who start smoking at 13, 14, and 15 are an important subgroup that are different than people who start smoking at 18. So I think that caveat needs to be included in any discussion.

DR. MENDEZ: So just to make a point, I understand all of that, but this is not people that started smoking at 18. This is an artifact that

says that this is the proportion of people at 18 who are smoking. It's not that they become initiators. They might be smoking since 12, but I am not paying attention to that fact. It's just, at 18, this is the proportion of people that are smokers in the different categories.

DR. BENOWITZ: Right. But my point is, if menthol has a selective effect at age 13, then it's going to have a different effect at age 18.

DR. MENDEZ: But at age 18, you see what proportion of total menthol you have, what proportion of non-menthol you have, and you go from there; so that's how the model tracks.

DR. SAMET: Mark?

DR. CLANTON: I'm willing to accept this 18 catch basket because I think the real issue you picked 18 is because if you're smoking by 18, you represent 90 percent of the people who are going to be chronic smokers.

DR. MENDEZ: Exactly.

DR. CLANTON: I understand that. Whether there's sensitivity analysis, cutting this model in

different ways, we may be able to do that. But given the fact that if you're smoking by the time you're 18, in fact, you're going to represent the balance or the greatest proportion of people who will be chronic smokers.

DR. SAMET: Dorothy?

DR. HATSUKAMI: In large part, I think what we need to do is take a look at the data that we currently have. And there isn't going to be a lot of data to help us make some of these decisions. So I hate to prematurely make these decisions without necessarily knowing the availability of some of the data.

So I just wanted to make that point as well, because you're right, Neal. I can only think of one study that talks about initiation and how that might -- the percent of people that initiated with menthol versus non-menthol, and how that relates to the probability of becoming established smokers, daily smokers, or dependent smokers. And that's in the youth population.

DR. SAMET: Again, I think the model will be

useful because it will -- to provide the input parameters, we'll have to gauge exactly how much evidence is available on these points, which I think becomes important. And I guess the only thing I can say in our ultimate defense is that we will look at the literature as carefully as possible and make the most informed judgments.

Cathy?

DR. BACKINGER: I had a question about how initiation is defined, and of course, prevalence. And I'm assuming that you're using smoking within the last 30 days.

Is that correct?

DR. MENDEZ: I will –

DR. BACKINGER: I mean, the reason I'm asking is I'm wondering if the data are available, and I think most of the national surveys ask about everyday, some days. So getting at the everyday smoker versus the some day, because mostly we just talk about smokers, and that's defined as smoking within the last 30 days.

I guess that's a question. I'm not a

statistical modeler, but trying to get at, truly -- and you can look over time about what proportion are smoking every day versus less than that. So I'm just throwing that out there as a question.

DR. SAMET: I think the model is generic, and I think, again, this relates to possible changes over time. And I think, Cathy, you're probably pointing to the fact that the picture, quote, "current smokers now includes perhaps more people in various categories of daily, non-daily," and so on, and that might change into the future.

Again, this is the kind of, perhaps, model adjustment that might be done in the future if we have the luxury to do it. I think, again, to go back to the famous quote about all models are wrong and some are useful, we're hoping for utility here, and I think we are not trying to, nor can we, capture every way that the world might turn in the future.

DR. MENDEZ: Let me make also a statement. Right now, what I'm using is what proportion of 18-year-olds are currently smokers. That's the

definition. What proportion of 18-year-olds are menthol smokers and non-menthol smokers? That's the idea.

The way that I've been informing my previous models are the definition of the current smoker from the have you smoked more than 100 cigarettes in your life and do you smoke now. So that's the definition I've been working off. But it's not how many people initiate at age 18, but what proportion of them are smokers.

DR. BACKINGER: Right. And I agree that for the purposes for today, trying to have more of a basic model. But I think at some point, in all of our spare time, looking at the daily smokers over time would be an interesting input for the model.

DR. MENDEZ: Absolutely.

DR. SAMET: Just make the point. I mean, one thing leads to another. And, of course, the relative risk estimates from CPS II were based around the good old-fashioned pattern of current smoking of 30 plus years ago. And, again, you're talking about what might be the health risks of

different patterns, though, moving into the future, so there are additional uncertainties.

But, again, I think what David has shown us is the structure of the model. I think we've suggested refinement, but I think we'll make it more useful for our report. I think we know our jobs, in terms of identifying the parameters, our best estimates, and the range.

Other issues that anyone would like to bring up with regard to the model?

[No response.]

DR. SAMET: Tim, anything else?

DR. MCAFEE: No, I'm fine. Thanks.

DR. SAMET: Okay. Good. Thank you, David, for all of the hard work to now, and even more to come.

DR. MENDEZ: Thank you.

DR. SAMET: Now, we're going to move onto the series of brief presentations on the industry documents related to menthol, and we're going to lead off with Topic 1, Brian Thomas, Dose Response Relationships with the Physiologic Effects of

Mentholated Tobacco Smoke.

Industry Presentation – Brian Thomas

DR. THOMAS: Thank you. I have a number of slides, and we have limited time, so I'm going to go through the slides very rapidly, and I apologize for that. However, I think most of you have seen the information that I'm about to present. The important disclaimer is that the content of this presentation comes from a review of industry documents performed at RTI under a contract with the Center for Tobacco Products at FDA, and as such, the content and conclusions of the presentation are not those of the Center for Tobacco Products.

The documents that I reviewed consisted of study protocols, study data, statistical analyses packages, study reports, a wide variety of documents. There are approximately 132 documents totaling 25,000 or so pages of information. There was a considerable amount of repeated information or entire documents which were frequently encountered. And some of the information was

deemed commercial confidential information, and that information will not be presented here.

So the first study I'm going to address is a total exposure study that consisted of approximately 5,000 adult participants. It determined the menthol status, the FTC tar delivery, gender, age, body mass index, race, education, income, U.S. Census region, number of years smoked, total puff volume, and number of cigarettes smoked per day in the study participants. They collected blood and urine samples and analyzed those for selected biomarkers of exposure; that's BOE, the acronym that I've come up with, that was used in biomarkers of potential harm.

The response variables for the statistical model that was used for the biomarkers of exposure and the biomarkers of potential harm was an ANCOVA analysis, a covariance model. The biomarkers of exposure were nicotine equivalents and carboxyhemoglobin levels.

The biomarkers of potential harm included a

number of clinical endpoints relating to endothelial function, inflammation, oxidative stress, lipid metabolism, and metabolism. And as I said, the statistical model factored in demographic factors as well as smoking history and behavior. The statistical significance was evaluated for main effects at P, less than 0.05 and at P, less than .1 for interaction terms.

There was also an estimate of the level of nicotine dependence, and they used the Fagerstrom test for nicotine dependence. And in that instance, logistic regression was used to compare the estimated level of nicotine dependence, factoring in, again, demographic factors.

So, first of all, I'll just make some quick observations about this, and it may not be immediately apparent, but you have to take me for my word that consistent with previous observations, African-Americans comprise a higher percentage of menthol smokers, approximately 43 percent, than non-menthol smokers, which they comprise about 7 percent in this study population. And also

consistent with previous observations, female smokers comprise a higher percentage of menthol smokers, approximately 64 percent, than non-menthol smokers.

Menthol smokers also appear to have a higher nicotine exposure per cigarette. I need to go through this quickly. You can see there tends to be a higher nicotine equivalent per cigarette in menthol than in non-menthol. However, this higher exposure could be related to the observation that African-Americans, which comprise a greater percentage of menthol smokers, tend to have a higher nicotine exposure per cigarette than whites with either menthol or non-menthol cigarettes. So you can see that data in this table below.

Menthol smokers appear to have a lower nicotine exposure per day, if you look at the numbers; however, this lower exposure could be related to the observation that African-Americans, which comprise a greater percentage of menthol smokers, tend to have a lower nicotine exposure per day than whites when smoking either menthol or non-

menthol cigarettes. So there are a number of variables that add to the covariance of the measure, the dependent variable that we're looking at.

I can go on. The lower nicotine exposure per day seen in menthol smokers could also be related to the observation that African-Americans, which again comprise a greater percentage of menthol smokers, tend to smoke fewer cigarettes than whites when smoking either menthol or non-menthol cigarettes.

Finally, if we look at carboxyhemoglobin levels, they were also observed to be slightly lower in menthol smokers as compared to non-menthol, which again could be a result of the non-equivalence in the study population between these two groups with respect to demographic or smoking behavior differences.

So you have to take into consideration these variables and their impact on the response variable of interest. And what one can do, then, is by using an ANCOVA model to account for the covariance

and other factors which may influence exposure, the results of the analysis revealed that -- and I quote the conclusion that was provided by the industry -- "In the total exposure study with 3,585 adult smokers, menthol status, menthol by race, and menthol by gender had no statistically significant effect on adult smokers' exposure to carbon monoxide and nicotine as measured by the following biomarkers," which I just described.

So without going into the same type of data tables for the biomarkers for potential harm, which there were many, again, in an analysis of covariance model, which included demographic smoking history and behavior variables, menthol status and menthol status-related interaction terms were not retained in the final models for any of the biomarkers of potential harm.

The industry concluded that in the total exposure study, there was no statistically significant effect of menthol status alone or menthol status interactions with other variables on these selected biomarkers of potential harm in

adult smokers. There is a poster, and they made the conclusion, "These results do not support the hypothesis that menthol cigarettes increase the risk of smoking-related diseases." That's a strong conclusion.

Next, as I indicated, the subjects in the total exposure study were asked to fill out a questionnaire that was used to estimate the level of nicotine dependence, the Fagerstrom test. And I've shown here the distributions for non-menthol in dark bars and menthol smokers in the lighter bars, and their dependence score from zero to 10, with these people being strongly addicted and these people having very low addiction. And one can see that the distribution is fairly similar between the two groups, which one would predict, then, that their mean scores between menthol and non-menthol smokers are approximately the same.

It was pointed out that one of the questions in the Fagerstrom test for nicotine dependence is how many cigarettes do you smoke. And as we've seen, the African-American population tends to

smoke fewer cigarettes. They're higher represented in menthol smokers, so one might expect that the scores may be skewed in some instances because of that one particular question. But, regardless of that, it was the means that was provided in this assessment.

If we look, then, at scores as they're differentiated across tar delivery categories, I would just point to your attention that in the menthol smokers, in the highest tar categories, the individuals in high addiction are apparently lower than what you see -- and I understand the numbers are hard to read -- in the high-addiction categories in the non-menthol.

When one looks at calculated scores, you can see that, actually, the mean value appears to be higher in non-menthol, in this high-tar category. The confidence intervals don't overlap. I would point out that, that is also the case in this lowest tar delivery category where there doesn't seem to be an overlap in the confidence intervals between these. But, again, there's more to it than

just the overlap of those particular confidence intervals because there's other variables that are contributing to the score.

Going to my notes so that I can get through this quickly, this slide seems to indicate that the dependence scores appear higher among Caucasians, menthol and non-menthol smokers, than in African-American menthol and non-menthol smokers. And, again, I think that has to do with the impact of the question as to how many cigarettes are being smoked by these individuals on a per-day basis.

I'm just going to quickly go through, and then I can finish.

Also noted was that there did seem that the scores appeared higher in higher age categories for both menthol and non-menthol smokers. And, in particular, there seems to be this one data point that they're higher in non-menthol smokers, aged 35 to 49. And to no one's surprise, I hope, the mean dependence scores appear higher with longer smoking duration for both menthol and non-menthol smokers. And again, there seems to be, perhaps, a slight

difference with respect to the scores for menthol smokers; they appear somewhat higher than non-menthol smokers for those with five to nine years' smoking duration. But this is, again, just looking at confidence intervals and not factoring in other important variables.

There didn't appear to be an association between smoking within the first 30 minutes after waking up and menthol. And here, the odds ratio was 1.17, and the confidence intervals did not go to where that would be a statistically significant effect. And this was adjusted for age, race, gender, education. So it was close, but it did not reach significance.

So I went through these results. I'll skip this. That was exactly what I read during each of the slides. The conclusion was that the summary statistics are in line with the NSDUH report and other recent publications which found no difference in dependency measures by menthol status. It concluded African-American smokers did not have higher dependence scores. None of the scientific

data appeared to support the hypothesis of menthol enhances the addictiveness of cigarettes.

As I indicated, there are some, perhaps, important caveats to that conclusion. I should point out, though, this one document stated that further testing for statistical significance is necessary, and I'm pleased to say that they did that. They used their logistic regression analysis to evaluate the effect of menthol-containing cigarettes on the score.

In the total exposure study, the models were adjusted for gender, race, and with respect to race, African-American versus Caucasian, age, annual household income, education level, and machine-measured tar yields. Again, the significant measured at P less than 0.5.

When they adjusted it, menthol status had no statistically significant effect on any single item of the FTND or on the overall score. So I think compared to non-menthol smokers, the data provide evidence that menthol -- this is, again, the conclusion in industry documents -- does not

increase nicotine dependence.

There was one other study that I'm permitted to share with you. This is an interesting approach to looking at some data, and I'll, unfortunately, read it directly from the slide. They took the Tobacco Institute Testing Laboratory in 1996 that was used, and they used the nicotine and carbon monoxide machine yields. And that's an important caveat. It's machine yields, and we know that people smoke differently than machines.

With that data in hand, they looked at 354 commercial non-menthol and 167 menthol brands. And they included it in the analysis, and they looked at the distribution of these yields, either nicotine or carbon monoxide, in 10 intervals, according to the percentage of the maximum yield for each parameter; so they characterized the distribution.

Then they took the fraction of each cigarette type and each cumulative percentage band -- this is very clear, I'm sure, to everybody -- and they calculated it on with their

difference. And then they used the K-S test, as I like to call it, the two-sample test used to determine whether two populations have the same distribution.

The theory behind this is that if the two populations of cigarette brands, menthol and non-menthol, have similar distributions of nicotine and carbon monoxide yields, it suggests that any difference in observed biological effects observed between the two populations are not attributable to differences in carbon monoxide or nicotine exposure. Again, I would emphasize the word "suggests".

Of course, here are exactly that interval data in 10 buckets. For nicotine, in this particular instance, milligrams per cigarette for non-menthol and menthol, and then the band fraction between the two different, and then they have the difference. And wherever the maximum difference occurs -- I believe it's in this instance, at the highest interval percentage. I can't see the data myself very well. But regardless, then they tested

this to see if there is a significant difference, using a Chi-squared comparison, and that's what the K-S test does. And, in this instance, there was not a significant difference between domestic menthol and non-menthol brands, and similarly with respect to carbon monoxide yields.

Again, it supports the null hypothesis that the two cumulative distributions are not significantly different between domestic menthol and non-menthol brands, and we understand what the implications are to suggest a conclusion from that.

That is the information that I have to share with you today, and I'll take any questions at this time.

DR. SAMET: So quick questions. Jack?

DR. HENNINGFIELD: Just a couple of quick observations. The test observations, those of the industry, frankly, in terms of evaluating addiction risk, it takes a simplistic approach. It ignores a lot of concepts of addiction, one of the many being that addiction risk is not simply related to the concentration or the dose of the drug. And, in

fact, a lot of our youth abuse problem with alcohol isn't with the highest concentration products; it's with beer.

It doesn't rule out the fact that African-Americans have at least as great a difficulty in success rates in cessation as Caucasians, while smoking fewer cigarettes per day. And menthol could partially or completely, by virtue of its powerful stimulus effects, explain that difference, but the test study cannot rule that out.

So what has been done in the test study is to very selectively look at different measures, and do tests, and then come to a global conclusion, which is not necessarily the sum of the parts. So I think we have to be really careful when we look at the global conclusions emerging from that study.

DR. BENOWITZ: I've got a question and a comment about these last two slides. I don't understand if the cumulative percentage band is supposed to be divided into 10 equal spaces, why is the band fractured in 21 percent in the --

DR. THOMAS: Well, it isn't. It's

actually -- it's the number of the percentage of all the products that fall within that specified band of the maximum yield. So however many products have a carbon monoxide yield of 7.9 milligrams per cigarette or below, comprise the band fraction of that first one, and then however many products comprise the band fraction between 10 and 20.

DR. BENOWITZ: I would say, first of all, that .55 is still reasonably high nicotine delivery, and I'd be very interested to know, especially since menthol is supposed to be particularly important with the highly ventilated cigarettes, to see what's going on below a nicotine delivery of .55. That is one thing.

The second thing, just to make it clear, we know there's an interaction between yields and smoking behavior. So the lower the yields, the less likely a person is to smoke, similar to the ISO protocol, so that these things are really not very helpful for actual exposures.

DR. THOMAS: I would agree with that.

DR. BENOWITZ: So I think we really can't use these data to conclude what was concluded in the documents.

DR. THOMAS: I would also indicate that this is 1996 data that was used, and as we saw earlier, and I think we'll see soon, the levels of both nicotine in per cigarette and in menthol have increased, perhaps mostly menthol.

DR. SAMET: Not to discourage this discussion, but let's move on. Thank you.

So the next presentation, chemosensory effects of menthol compounds in tobacco smoke. Hernan?

Industry Presentation – Hernan Navarro

DR. NAVARRO: Here is the topic title, and some industry documents submitted to the FDA. As Brian said earlier, the purpose is to inform TPSAC regarding the impact of menthol in cigarettes on public health. And all the work recorded in this presentation was done under contract with the Center of Tobacco Products at the FDA, but the contents are out of RTI.

The industry documents that I reviewed with

one person at work, 885 pages. There were 72 documents that were listed, 58 documents total. There were two of the same. There were 12 duplicates, and 18 were deemed not useful.

The types of documents, there were memos, protocols, reports, PowerPoint presentations, publications, figures, letters, and a literature review. And, as I said earlier, all of the documents were reviewed by me and one other researcher at RTI.

A summary, the industry provided information. It's all considered commercial, confidential, and it cannot be presented during this session. So there is no information to present. Sorry.

DR. SAMET: I hesitate to ask, are there questions?

[Laughter.]

DR. NAVARRO: Are there any questions?

DR. SAMET: Thank you.

Okay, moving right along to Ken Davis, Understanding the Summary of Industry Responses to

Topics 11 and 12.

Industry Presentation – Kenneth Davis

MR. DAVIS: Good afternoon. This presentation is on, as we said, the summary of industry responses to Topics 11 and 12. It was prepared by myself and Dr. Poonam Pande, Richard Daw, and Michael McCleary. All of these people added substantially to this presentation. And here is, indeed, my disclaimer slide that the contents and conclusions of this presentation are those of RTI International, even though this was prepared under contract to the FDA. Some information here was deemed commercial or confidential, and that information will not be presented in the open session.

The topics, Topic 11, deals with menthol and nicotine in the cigarette, and quantities of menthol and nicotine in the cigarette by brand, and sub-brand, and by year between 2000 and 2010 for menthol and non-menthol products.

Topic 12 dealt with the quantities of menthol and nicotine in the cigarette smoke as

determined by the Cambridge Filter/ISO test method using standard parameters, as well as the intense smoking conditions set forth in Canadian regulations by brand, and sub-brand, and by year between 2000 and 2010 for both menthol and non-menthol products. Virtually, all of this presentation deals with data that was generated by the Cambridge Filter/ISO method, as there was very little data presented for the more intense test methods.

There were limitations that we observed to the data. If you can imagine a matrix of data that has 575 or so brands and sub-brands down the vertical axis, and 11 years across the horizontal axis, it would be very comforting if that had been full and every cell filled. But that was not the case. There was a good bit of data there that was not there. There were brands that data was reported for early and not late. There were brands that data was reported late, but not early. And we need to remember, in the midst of all of this, that responses to Topics 11 and 12 were voluntary on the

part of the industry.

The data for the year 2010 is incomplete, and it was submitted through June or July. It's not a complete year. Another factor is that multiple units were used for reporting nicotine and menthol between brands.

The general procedure for the summary of responses for Topics 11 and 12 is described in this slide. Our source document for this work was a large spreadsheet workbook that was prepared by the FDA and that we used for our subsequent work. We took steps as outlined in these bullets. I don't think I need to go through all of those.

We extensively used auto-filters on appropriate columns in the data, and auto-filters and other methods of isolating data that we wanted to obtain for this summary. We used the built-in statistical functions of Excel to calculate averages, means, count of items, standard deviations, et cetera, and to perform the specific summaries. And we did use the graphing functions of Excel for this purpose.

From a high-level view of the data, the industry submitters provided information and/or comments on 561 brands and sub-brands in response to this question. And with your permission, from now on, I'm going to say brands.

Industry submitters responded with data in some form on 413 cigarette brands. They provided menthol content data for 343 brands over 2000 to 2010. They provided nicotine content data for 122 brands during that time period, of which 68 were listed as menthol brands and 54 were listed as non-menthol brands. They provided menthol content data for 263 brands in the year 2009. 2009 was the year for which the largest number of data points was available. They provided nicotine content data for 104 brands in 2009; 71 of these were listed as menthol brands and 33 were listed as non-menthol brands.

Units of measure used for reporting nicotine were milligrams per cigarette and milligrams, also percent on a dry weight basis and parts per million. In this summary, milligrams is assumed to

be the same as milligrams per cigarette. The units of measure used for reporting menthol content were milligrams, milligrams per cigarette, milligrams per pack, and 15 other units, some of which refer to filter types. And this was a significant complication to our analysis of menthol data. The units' milligrams per cigarette and milligrams per pack were separately treated in our summary, and the unit milligrams is assumed to be the same as milligrams per cigarette.

Here is a summary table of the data that was provided in response to Topic 11; that is, in cigarettes, not in smoke, but in cigarettes, the nicotine in menthol cigarettes ranged from a value of 12.5 milligrams per cigarette, and please observe that the table is prepared in terms of milligrams per cigarette, except where noted otherwise.

We started in the year 2000 with a value of 12.5 milligrams per cigarette and stayed fairly close to that all the way through the time period. And in 2010, this value was 11.98 milligrams per

cigarette. There were no nicotine in non-menthol cigarette values reported in milligrams per cigarette during this time.

Menthol in menthol cigarettes ranged in 2000 from 0.61, and then there are some blank years, and coming to 2006, 2007, we had a much significantly higher number in the 7s, and then dropping down to the 4s. I just need to remind you that this data was spotty and not always satisfying in terms of its internal consistency here, but that is the data that we analyzed.

Menthol in non-menthol cigarettes ranged from a value of 0.1 in the year 2000 and finished in 2010 with a value of 0.1. Menthol in menthol cigarettes in milligrams per pack you see started in the year 2000 with a 4.41 and was fairly consistent through 2006. Beginning in 2007, there was a very significant jump to values around 8. Menthol in non-menthol cigarettes began to be seen in the year 2010, measured in terms of milligrams per pack at 7.43.

This is that same data presented

graphically, and I have highlighted here with the green oval the increased menthol values in the latter part of the time period from 2006 to 2010. For Topic 12, we're now dealing with menthol and nicotine in smoke. Industry submitters responded with some information on 468 cigarette brands. They responded with menthol content data for 198 brands over the time period. Of these, 142 were menthol brands, 55 were non-menthol brands, and 1 was unspecified.

They provided nicotine content data for 464 brands; 255 of these were menthol brands, 194 were non-menthol brands, and 15 were unspecified. They provided menthol content data for 106 brands in 2009, and remember this was the year in which the most data was available. And they provided nicotine content data for 322 brands in the year 2009.

This is a summary table of the data that we analyzed, beginning with nicotine in menthol cigarettes. And, again, this is presented in terms of milligrams per cigarette. We had a value of

0.91 milligrams per cigarette in the year 2000, and ended up with a value of 0.89 milligrams per cigarette in the year 2010.

Nicotine in non-menthol cigarettes began with a value of 0.85 in the year 2000 and finished up with a value of 0.86 in 2010. Menthol in menthol cigarettes in the year 2000 was 0.58 milligrams per cigarette, and it continued with similar values through 2009. In 2010, we did observe a higher value of 0.83. And menthol in non-menthol cigarettes, again, shows up in the year 2010 with a value of 0.14.

This is the same data presented graphically, and, again, I highlight with the oval the increased menthol values as seen by the green bar and the appearance with the little purple bar on the right of menthol in non-menthol cigarettes during this year.

That is the end of my data. The remainder of it is, as we said earlier, commercial confidential.

DR. SAMET: Jack?

DR. HENNINGFIELD: A quick question. You showed a dramatic increase in menthol per pack over about the last five years. Why do you think that happened?

MR. DAVIS: I don't know. There could be differences in manufacturing techniques. There could be any number of explanations. And as I stand here right now, I would simply be speculating if I answered that.

DR. SAMET: Dan, to his point?

DR. HECK: I could speculate on that. I know that with the advent of the reduced-ignition cigarette papers in that time frame, there were instances that I know some companies had discussed with the FDA, where the other design changes in the products were instituted to maintain stability, basically to bring the tar yield back down where it started before they used the banded paper.

Some of those changes, such as change in filtration and porosity and ventilations, were accompanied by a raising of the menthol levels in some products. But you have to look at the

specific products to answer the question definitively.

DR. SAMET: Patricia?

DR. HENDERSON: Actually, it's slide 9, on how you showed -- there's a discrepancy of -- well, actually, they're very similar in terms of menthol in menthol cigarettes, and menthol in non-menthol cigarettes.

This is in tobacco, right?

MR. DAVIS: No, this is in smoke.

DR. HENDERSON: In tobacco? And then --

DR. SAMET: That is in tobacco.

DR. HENDERSON: Right, in tobacco. But then it drops down to – for smoke, it drops down -- I guess I just don't understand what is happening, if for tobacco, it was similar, quite similar, and then -- does the menthol just kind of disappear or where does it go?

MR. DAVIS: First of all, let me apologize for my confusion between the two very similar-looking slides. This is the one in smoke here, and slide 9 is in tobacco. You're talking about the

tobacco one?

DR. HENDERSON: Right. So it's 8.01 and 7.43, right, for the last year. And then if we go to smoke, the menthol levels go from .8 to .83, and then from 7.3 to 1.4. I'm just wondering why there's such a big drop.

DR. HUSTEN: I think we need to remember these were voluntary submissions, and it depended on -- the same companies may not have submitted across all tables.

DR. HENDERSON: All right.

DR. HUSTEN: I believe that's true.

MR. DAVIS: And I think that some of the explanation may lie to what was said here a moment ago.

DR. HECK: I would caution all of us, given that these are a variety of brands, we're not able to know today, we shouldn't put too much stead into these mean to median numbers until we really understand what is driving them.

DR. SAMET: Neal?

DR. BENOWITZ: I have a question for Dan. I

don't understand what was meant by menthol in a pack. How's that measured? What does that mean?

DR. HECK: Yes. That may be a term of art. But I think in the most common usage, when the menthol cigarettes are produced, if a quality assurance unit or whatever is monitoring the menthol in the product, as it goes out the door, let's say, the menthol, as you know, partitions around among the components in the product. And some manufacturers add it to the packaging; some add it by different methods to the tobacco. So to really capture all of that menthol for measurement purposes, you would basically extract the entire cigarette, the filter, the paper, the tobacco, and do a chemical analysis of the menthol.

You might express it per milligram tobacco or per pack, depending on the company's practice. But you're trying to capture all of that menthol that may have exchanged between packaging and paper and tobacco.

DR. BENOWITZ: So what I don't understand is how can you have an average menthol per pack of

8 milligrams, an average menthol per cigarette of 4 milligrams when there's 20 cigarettes in a pack? It just doesn't add up.

DR. HECK: Again, it depends on the nomenclature used by the company in question. I know that the Lorillard Tobacco Company uses the term pack menthol, but that doesn't represent the total quantity of menthol in the pack. It may mean a different thing depending on how different companies do their analyses and quantify it.

DR. BENOWITZ: So it sounds like our committee really can't use that for anything when we don't know what it means.

DR. HECK: I would suggest caution here. I think individual companies might elaborate on some of these figures if there's interest, but I'm unaware of any general or large trends in menthol usage within the industry, with the exception of the adjustments to product design accompanying the reduced-ignition paper, which in at least some brands required additional levels of menthol to achieve the same menthol level in the smoke because

of other design features, such as air dilution, ventilation, changes in filter efficiency.

DR. BENOWITZ: I've got another question about just how reliable the data are on menthol, non-menthol cigarettes. The reason that I ask that is that if you look at what's in the menthol cigarette, say it averages 4 milligrams, and then you see menthol in the smoke, and say it's .6 to .8, well, that is consistent with the known transfer efficiency of like 10 to 20 percent. That's fine.

If you look at menthol and non-menthol cigarettes, and the actual cigarette itself was .10 and the smoke was .14, there's no way that you can have 100 percent transfer efficiency. So I don't understand how -- that doesn't make any sense to me.

MR. DAVIS: All I can tell you is that we analyzed the data that was available, and these are the numbers that it produced.

DR. BENOWITZ: Dan, can you explain it to me?

DR. HECK: No. But today I had a similar question slide number 9, where the very last figure in the lower right of the table is 7.43 milligrams per pack for a non-menthol cigarette. That's, as we see, very similar in magnitude to the menthol cigarettes presented here.

So I really think it may be an anomaly, based on perhaps one submitter or one brand. It just seems too high to me as well, because it looks almost the same as that in the menthol brands. And, intuitively, it seems like that can't be accurate, but I just don't know.

DR. SAMET: Okay. Thank you.

I think what we're going to do before we take the break is finish up with the last two presentations. There's one on Topic 8 and one on Topic 9. And for some reason -- let's see, we have one of them listed twice, but I think what we'll do is have Dr. Hersey present Topics 8 and 9 before the break.

[Pause.]

Industry Presentation – James Hersey

DR. HERSEY: If it's okay, let me proceed with Topic 9 because this is fairly short, and then I can cover Topic 8 when we deal with response to questions. So I'm going to start with the standard disclaimer. This is Topic 9, which we reviewed like 87 documents. This is probably the third slide in.

What we did, we're looking at topics related to initiation of tobacco use. And so we looked at analysis of cross-sectional data, which we presented earlier, some estimates of menthol smoking by age, grade, which was presented and I'll cover again in response to questions, and some limited data from industry studies.

Specifically, I got one '96 menthol marketing study. We reviewed some output. This study came from a larger marketing study reported in the Menthol Fact Book. When I read the methodology for that, this is a telephone survey stratified by urbanicity. They don't tell me the response rate.

What they did was survey menthol smokers,

and what they do is really compared smokers of Newport menthol cigarettes to a grab bag of what they called low-tar menthol cigarettes, which are other kinds of -- it covered more than just Lorillard. It would have covered all the low-tar cigarettes under menthol cigarettes; so this data here on kind of an age gradient.

Newport is much more commonly smoked among 18- to 24-year-olds than, say, low-tar menthol; data on race/ethnicity. Again, as you'd expect, Newports are pretty common among whites. Low tar menthol is much more common among -- I mean, Newports is more common among non-whites and low-tar menthol is much more common among non-Hispanic whites. Then in terms of education, 70 percent of Newport users had a high school education or less.

The most interesting finding to me on this study was one, cigarette first smoked; level of smoking, again, Newport smokers. Again, they compared that to the low-tar cigarettes. So 32 percent of Newport smokers are smoking less than a pack a day. And those smokers of low-tar menthol

were smoking more packs of cigarettes per day, or more of them were smoking one or more packs a day.

The majority of Newport smokers, 66 percent, reported that the first cigarette that they ever smoked was a menthol cigarette. And that's much lower, only about 42 percent among people who are smoking low-tar menthol cigarettes.

That's basically what we had in this little piece of the presentation.

DR. SAMET: Yes, Neal?

DR. BENOWITZ: Just a quick question about the yield of Newport versus low-tar menthol cigarettes. Is Newport considered to be a high-tar cigarette, or medium-tar, or low-tar? How does Newport compare?

DR. HERSEY: That was not explained in the industry documents, so I can't answer that from what I read.

DR. HECK: Newport does have -- the most popular variant is a full-flavor or a higher-tar cigarette, but it does also have a low-tar. There's a lower-yielding Newport as well, usually

called the light.

DR. BENOWITZ: So in terms of market share, though, if you're saying that 30 to 40 percent are smoking Newport, is most of that going to be the high tar?

DR. HECK: Yes. Certainly, at the time this was -- was it '96 that I see as the date?

DR. HERSEY: Yes, '96.

DR. BENOWITZ: Okay.

DR. SAMET: Other questions on this mini-presentation?

DR. HERSEY: We had one question. I'm now going to turn to a response to a question, which answered on Topic 8 from Eric Johnson about denominators. And this is a real short answer, which was covered some in this closed session this morning.

These data come from a 1991 study reported in the switching book. And among adults, because this sample is 21 years of age and older, switching is not all that common, only about 9 percent of young people who are smoking. And so let me try to

explain what I can about your denominator question.

So we calculated the denominator, overall, about somewhere around under 9 percent of adult smokers reported switching from one brand to another.

Now, I'm giving you a couple of percentages here. The first one is really on your left, which is the 7.7 percent. So these are smokers of non-menthol brands who make a switch to any other brand of cigarette, so they can switch from Marlboro regular to Camel regular. But of those people who initially were smoking a non-menthol brand, whatever brand they would have switched to, 7.7 percent subsequently switched to a menthol brand.

The next column over really represents the universe of people who switched who started out smoking a menthol brand of cigarette; these are adults. So any menthol smoker who went from one brand to another, whether it was Kool to Salem or Kool to Marlboro -- but any switch like that from a different brand, 26 percent of those switches were

from a menthol brand to a non-menthol brand. So among adults in this group, the switching was more common from a menthol brand to a non-menthol brand than some other kind.

Finally, another way to look at, basically, the same data, just calculated a different way, in this case, the denominator here in these two is everybody who made a brand switch in the past year. If I made a brand switch from one brand to another, 5.7 of those people who made a brand switch moved from a non-menthol brand to a menthol brand, and 6.9 moved from a menthol brand to a non-menthol brand. So it's the same numerators. The denominators switched some. I hope that answers your question.

DR. SAMET: Okay. If that was our question, I think it's answered.

[Laughter.]

DR. SAMET: Let's see, questions about the answer to our question?

[No response.]

DR. SAMET: Did we cover everything or did

we have one more?

So these are items that were scheduled for half of the public comment session. We thought we would just finish these off.

Industry Presentation – James Hersey

DR. HERSEY: Good. This gives me a chance to respond to some questions, which were asked already about presentation number 9. And we're really looking at comparative rates of initiation by menthol or non-menthol use. This represents some analysis that we did in response to that question of NSDUH data between 2004 and 2008. And, again, this is work done by RTI, not by FDA, so we're responsible for this.

We were trying to answer two questions. The first is, is there evidence about an age gradient in proportion to younger smokers who smoke menthol versus non-menthol cigarettes? And I'll hit that first.

The second question is, what are the characteristics of smokers of menthol and non-menthol cigarettes? So let me hit the first

question, which is really about age gradient. When we look at the issue of age gradient, what we did was combine NSDUH data from 2004 to 2008. And we broke them into those data by age groups, 12 to 13, 14 to 15, 16 to 17, and 18 to 19.

It does appear to be -- oh, and just to be clear, these are data based on those people both who are current smokers within the last 30 days, and also who could tell us whether they smoked a menthol or a non-menthol cigarette brand.

So among 12- to 13-year-olds, among those current smokers, 48 percent of them were smoking menthol. It drops to 46 percent among those 14 to 15, 43 percent to those 16 to 17, and 33 percent of those 18- to 25-year-olds. So there does appear from these data to be an age gradient within the under-17-year-old age group.

In this slide, I simply showed you a breakout by two age groups to give me a larger sample size, 12 to 14, 15 to 17. And, again, I've given you the proportion of all smokers who report that I'm smoking a menthol cigarette; and, again,

those data by male and female and by race/ethnicity.

The race/ethnicity data are probably interesting because among those 12 to 14 on whites and among Hispanics, those numbers are higher; the percentages are higher among 12- and 14-year-olds than they are among 15- to 17-year-olds. Among whites, for instance, 42.7 percent of current smokers could identify their brand, so they were smoking a menthol brand. Among 15- to 17-year-olds, that number was 38.1 percent, and it was a similar trend among Hispanics.

Among African-Americans, this actually goes the other direction. So they're switching -- I don't know if they're switching because this is cross-sectional data, but 15 percent of African-Americans who are 12- to 14 years old are smoking menthol cigarettes, and this goes up to about 70 percent among those who are 15- to 17-year-olds; so much more popular menthol use among that older group.

You have a similar pattern but a lower prevalence level among the other group. Now,

remember, this other group would include Asian-Americans and Pacific Islanders where menthol use is really common.

We had one question from a panel member, how did our estimates differ from some of the estimates we found in industry documents? This comes back from that original slide so you can refer to that. But there's really two kinds of things. There are differences in denominators. Often, the industry would report three groups, so it would report people who did not know whether they smoked menthol or non-menthol. If you include those people in the denominator, you've got a somewhat lower percentage. And there was also some differences in time interval. The industry data we quoted was 2008, and the SAMHSA estimates were 2004 to 2008.

Just so it's pretty clear what those differences are, let me give you an example of denominators because the trick on this is -- by age group, when you look at the 18- to 24-year-olds, the top set of graphs show kind of menthol, non-menthol, I don't know, or didn't report, versus the bottom two

just show two categories based on people who knew or didn't know.

So once you get pretty established smokers, 18- to 25-year-olds, there really isn't much difference. You've only got 1.4 percent of people, smokers, who didn't know or report whether they smoked menthol or non-menthol.

Among younger age groups, you're going to see a bigger difference in your percentages. Among 12- to 13-year-olds, 13.4 percent in NSDUH, between 2004 and 2008, did not report whether the cigarettes they smoked were menthol or non-menthol. So I think it's important, when you interpret the data, to be careful, particularly at younger age groups.

The next question I'd really like to begin to answer is, what are the characteristics of youth who smoke newer brands? Let me start with a question I got from Mr. Hamm, who originally asked, on a graph like this, slide 10, an earlier version showed some Newport non-menthol people. As it turns out, NSDUH allows you to say, do you smoke menthol or non-menthol, and you can't cross that,

and so you have some misclassification. A later version of the graph of the same presentation is this one here, which doesn't include that Newport regular, so similar kinds of trends, but this data is cleaner.

The next question, again, the same topic; what are the characteristics, particularly of the people, Marlboro menthol, Camel menthol, those newer cigarettes, who is smoking them? Are they getting at new smokers or are they really just involving brand switching from one kind of brand to another?

I don't have all the answers you want, but let me tell you what we have found and share that with the committee. First thing we did in response to your questions was to look those data by race/ethnicity. And, again, don't get lost in the colors, the dotted red lines are non-menthol, the green lines are menthol, and I've got my four race/ethnic groups.

In this case, this is smoking of Marlboro menthol -- or Marlboro non-menthol. And so what

you see among whites, which I guess is in the top left, among Hispanics below them, and among the other group, which again is including your Pacific Islanders and Asian Americans, the use proportion of those current smokers who are smoking Marlboro menthol is increasing over time.

The proportion of people in those race, age groups who are smoking Marlboro non-menthol brands is decreasing over time for whites, Hispanics, and the other races. Blacks, those numbers bounce around, but, again, those percentages are much lower in any case.

We also repeated the same graph for Camel. We're looking at Camel menthol and Camel non-menthol products. This one is interesting because in all four race/ethnic groups, the green line, the Camel menthol, proportion who are smoking Camel menthol, increases between 2004 to 2008, and, in some cases, that increase is noted after 2006.

So you've got that increase going up there, and in none of those groups is there a big decrease in the red line on the top, the Camel non-menthol

products. So in this case, if Camel is absorbing people, it's either new smokers or people from other brands, but not from Camel menthol, a likely interpretation of those data.

Finally, this last graph shows smoking of Newport. And this top line is African-Americans. And then you've got, below that, Hispanics, and others, and whites at the lowest. But all four of those lines are pretty steady, so that the proportion of smokers who are smoking Newport doesn't seem to change very much.

Now, the next thing I did was take a look at some of these data by age and sex. And so, in this case, these are data for 12- to 17-year-olds, and I repeat them again for 18- to 25-year-olds. And this is year-to-year data.

These are data for who smokes Marlboro menthol, and what's going on is that among females and among males in this 12- to 17-year-old group, you have an increase in smoking of Marlboro menthol during that period, and it's particularly high among females. Again, you've got a similar

increase, though at a lower level, among 18- to 25-year-old groups. So if you are looking at who's getting targeted or what are the characteristics of smokers of these brands, women, or young women, are certainly a high target.

In the interest of time, I'm going to speak real quickly to this slide, the apologies to the committee. The right-hand column on the printed version messed up rows and columns. This graphic up above is correct. But all that really matters here is that among Marlboro menthol smokers, 58.5 percent of them were women.

Finally, I want to close with two other slides, which really look at the question about are we getting new smokers among these new menthol cigarette products. And, in this case, we looked at young people who smoked 100 cigarettes or less in their lifetime or more than 100 cigarettes in their lifetime, so kind of lifetime cigarette smoking, typically your definition of established smoking.

We did this with 12- to 17-year-olds and 18-

to 25-year olds. And, again, you've got a nice increase among those who smoked in the first row, 100 cigarettes or less. That percentage of people smoking Marlboro menthol increases from 13.6 percent, moves up to 19.7 percent, so a nice, big increase.

There's also an increase, but not quite as big, among people who smoked 100 cigarettes or more. Again, you have an increase among 18- to 25-year-olds, but, again, not as big as the increase among those 12 to 17.

Let me close with one last slide, where I took the same data and simply reversed the rows and columns. This is data from everybody who's 12 to 17 years old, and a current smoker, and you smoke Marlboro menthol. What are your characteristics?

So this shows the proportion of people who smoked 100 cigarettes or less. In other words, more than half, about 51 percent of smokers of Marlboro menthol that smoked less than 100 cigarettes in their lifetime, among those 18 to 25, is 48 percent.

Compare my figure of half of my Marlboro menthol smokers among those 12 to 17 years olds, have smoked less than 100 cigarettes in their lifetime, so they're relatively new smokers; only 38 percent of smokers of Marlboro non-menthol are in the same group.

You get a similar finding for Camel, even more striking perhaps; 62 percent of young people, 12 to 17 who are smoking -- of all Camel smokers. So this is my denominator, so my number looks bigger, but it's an interesting comparison this way. Among Camel smokers who are 12- to 17-year-olds, 62.1 percent are smoking 100 cigarettes or less a day, compared to 48 percent of those who are smoking Camel non-menthol brands, and then the bottom line shows Newport.

So those were the data that I had, and I thank the committee for very intelligent questions.

DR. SAMET: Okay. Thank you for your informative presentation. Let me ask if there are questions. And thank you for the slides, which we will take a close look at.

Questions? Dan?

DR. HECK: Just a quick observation, then a question. I think we heard from the marketing presentations back in July, I guess, that a new brand introduction, as you described them here, are not infrequently accompanied by price promotion activity that would put these national brands competitive with, let's say, a generic or something like that. So I think some of that switching may not be captured in these major brand surveys.

The question with regard to NSDUH survey, particularly ones of the underage smokers who shouldn't legally be able to purchase cigarettes, so they probably source their cigarettes in some irregular combination of friends, family, and some are probably purchased underage, does the wording of that question on menthol preference allow us to discriminate the young adolescent smoker who may be a mixed menthol/non-menthol smoker, might have smoked a menthol cigarette or two among others in the prior month? Can it enable that kind of discrimination?

DR. HERSEY: I expect from the data we saw about people who didn't answer that question, what's your usual brand of cigarettes, was higher the younger you were. So I suspect there is some noise in that data, and it's probably noisier the younger you get.

What I'm not as convinced -- but while the age would seem, to me, to lead to some greater variation in my estimate, which might not be reflected here, which simply shows a confidence around the sample size, it doesn't explain to me as well why I would claim to smoke Marlboro menthol versus Marlboro non-menthol. But it might get into something if you went to a lesser-known brand like a Misty menthol.

DR. SAMET: Okay. Other questions?

[No response.]

DR. SAMET: Okay. I think we look ready for a break. Let's try and do roughly 10 minutes, and then reconvene for the public hearing.

(Whereupon, a recess was taken.)

Open Public Hearing

DR. SAMET: We're going to get started with the open public hearing. And I'm going to read the comments about this.

Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency of the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with a sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

So just as a reminder to the speakers, you're allotted seven minutes each. There will be a light signaling you as your time comes to a close. Our first speaker is a familiar face, Greg Connolly, from the Harvard School of Public Health. Greg, welcome.

DR. CONNOLLY: Good afternoon. And I want

to say I got up this morning. I felt a little ashamed coming down because I had resigned from this committee, and I had left some experts, scientific colleagues, and people with great moral courage. And I have enjoyed very much serving on the committee.

On a personal note, I think I can contribute more to the committee by advising you on our 10 years of research at Harvard on tobacco industry documents, and I would also invite RTI up to Harvard, if they get a chance, on menthol in particular. We've published five articles. I'd ask you to read them. I've submitted articles to you today.

I want to present today quickly on a new study we did on menthol in Japan. And why is menthol in Japan interesting? It's because Japan in 1985 was a closed market. There was no menthol, and women's smoking was about 4 percent. The United States government compelled that country to open its market to Philip Morris, Brown & Williamson, and other U.S. companies, who quickly

introduced marked menthol with the intent to market to females.

I want to present, one, industry intent documents, their intent to marketing on women; number two, how they introduced specifically-designed mentholated brands for young females and what the impact was on initiation among young females.

These are quotes. They're in the paper. You can read them. I supplied them to you. But I think this is probably the best. This is from a Philip Morris focus group in Asia. The last statement is, "New starters usually cannot adapt to brands like Marlboro, Camel, 555. Menthol cigarettes are much less strong in strength and easier to adapt with". And we see brands for a very low menthol yields with low nicotine, and, more recently, we've seen brands introduced in Japan with menthol black, which has a high-impact, high-menthol load.

So menthol has two different effects. When people from RTI were talking about menthol, menthol

is not one product; it's multiple products with different levels for different effects on different population groups. That's in the industry documents.

This slide is difficult to read, but Philip Morris says here, "We have Salem Pianissimo." This is for the real feminine, young, starting female. The next two we have with the females sort of entering the workforce, and then finally, the virile female, the female that wants the high-menthol brand. One is the Pianissimo, one is the Virginia Slims Lights, and one is Marlboro Lights.

Brown & Williamson, BAT, was kind enough to do reverse engineering in the internal documents. And what do we find? We find, on the low-menthol, .01 nicotine per puff, but the menthol load is 1.38. When we go to the virile female target, that group of people who want a higher yield of nicotine, the nicotine level has almost gone up eightfold, and the menthol level has dropped almost 40 to 50 percent.

So we see a specific targeting in Japan to

create female smoking through the manipulation of menthol and targeting of high-menthol brands with low nicotine yields with the intent -- and it's almost a graduation strategy -- to bring those persons, once accustomed to the strength of the nicotine -- and keep in mind, nicotine is an irritant, and menthol provides the ease of dosing.

The one thing I can say after listening to the last hearing, you can keep this much more simple. The question before this group is does menthol initiate? And comparing Marlboro Lights with Camel Lights and menthol is not the right way to go. It's comparing Kools and Pall Malls with Newport. Marlboro Lights and Camel Lights are as good as any mentholated brand for initiating youth, and comparing the two, to me, is nonsensical.

Well, what happened in Japan? This is the menthol brand preference we saw from '96 to 2000. And these are junior high school seniors, so they're 12 to 14 years, ages. Smoking prevalence jumped from about 6 percent to 8 percent. Menthol use was around 50 percent among young females.

That's the best data we have in Japan.

Unfortunately, if I was in Japan at the time, I would have commissioned a longitudinal cohort study to assess the impact of the introduction of brands, and I'm sure we'd have a much richer database. But this only adds to data that we had before. Then we look at age cohort studies. Older females did not take up menthol; younger females did.

Now, I did work with Korea. And, in Korea, we established effective public health strategies to prevent the introduction of new brands. Menthol never took off in Korea, nor did female smoking. Female smoking still is at 3 percent. Menthol market is around the same level. Here in Japan, the menthol market now is about 20 percent.

If we look at U.S. studies -- I supply this to you from the internal documents -- we find the exact same thing, low menthol levels allowing the ease of initiation. Once initiation occurs, we can see bouncing up a person to a higher mentholated brand.

So the Japanese study, once again, is Japan. We can't compare it to the U.S. But it provides us a very nice insight into a market that didn't have menthol. And keep in mind, the United States is one of the few countries in the world with menthol, and the cop, the WHO, has recommended banning menthol.

Now, for the United States to keep up with the world, we should take maybe seriously the WHO recommendation. We are one of the few countries in the world to have mentholated cigarettes, the Philippines, Nigeria perhaps, but you do not see them in other countries. What is the big deal here?

Dorothy, Jon, others, asked about measuring menthol effects. So I just introduced to you some really nice documents that the industry I'm sure has produced under the questions that were raised by the group. And they included sensory panel, descriptive analyses, correlation requests. These are all in your documents.

I didn't see these appear with the RTI

submission, and if the industry -- and I'm sure they complied with this -- failed to comply with this, I would urge the FDA to act with the appropriate fines to make sure there's adequate compliance with the requests of this committee.

One thing -- let me just read to you, the menthol cigarette liking analysis modeled by Philip Morris. They call it M Claim. "To facilitate use, the neural network model of cigarette liking has been incorporated into the ultralux-based decision support system for analyzing and predicting the relationship between cigarette analytics and liking." And it goes on and talks about a C model.

Those models should be before the FDA today. And if they have not been submitted to the FDA, then it's time the FDA takes this industry on like any other drug industry and takes appropriate action to act.

I thank you all for your scientific expertise, but most of all, for your moral courage. Any questions, I'd be happy to answer.

DR. SAMET: Great. Thank you, Greg. And as

a former committee member, you got an extra 10 seconds.

[Laughter.]

DR. SAMET: And, of course, we're very appreciative of your contributions, and thanks for your introductory remarks.

DR. CONNOLLY: I am appreciative of your leadership, truly.

DR. SAMET: So let me ask for questions from the committee for Greg.

DR. CONNOLLY: Let me say, I have no financial interests to report.

DR. LAUTERBACH: Could we go back to Dr. Connolly's second slide, where he determined the menthol level or recorded the menthol level on the Salem Pianissimo?

DR. CONNOLLY: Could we go back to that slide? I didn't determine it. It was determined by BAT.

DR. LAUTERBACH: Okay. You have there, right (unclear) percent menthol, and the Salem Pianissimo at 1.28 percent of tobacco weight, no

doubt, for a cigarette, which was probably about a 1- to 2-milligram FTC tar at the time, right?

Now, you're claiming that's unusual, but I think if you look at similar data, which I know you have because you looked at the Brown & Williamson tobacco competitor brand reports, as reported in the article from Tobacco Control in the summer of 2010, I believe it was, I think you'll find that some varied U.S. cigarettes of the same delivery were at that menthol level, if not more, but the sales of those cigarettes were no great shakes. So, obviously, saying that's an atypical menthol, for a 1-milligram product is very misleading. It's very typical for a 1-milligram product.

DR. CONNOLLY: John, I'm glad you read my research, and I just hope the other committee members do so. And also, I specifically came down today to make sure that you weren't sleeping.

You know what's interesting is that this is Philip Morris's claims, not my claims. This is Brown & Williamson's data, or BAT Co.'s data. The menthol levels here are very low, and it was

interesting to note, to look at these lows, and compare them to, say, a Newport or a Kool, Newport being maybe .4 or for Kool, .8. But they are very low. But I think what it demonstrates is easing one's product into the marketplace.

The Japan market was traditionally a carbon market, a carbon filter market that extracted menthol, so all of these brands you see today are non-carbon brands. They were brought in totally new. Young women in Japan didn't cut off the carbon filter and then sprinkle menthol in a cigarette to become initiated, that there was an intention here by the companies to target specific cohorts within the female group, with, again, very low levels of menthol, and then graduate up to higher levels of menthol at the time.

I hope that answered your question.

DR. SAMET: Dan?

DR. HECK: I'm just wondering what relevance I can find here from a tobacco manufacturer, Philip Morris International, that doesn't do business here in the U.S.A., on a non-USA population, with some

very unique characteristics, including the advent of the dissolution of the government tobacco monopoly there and the introduction of a lot of foreign brands in the area you spoke of from the multi-national companies.

What relevance does it have to our question?

DR. CONNOLLY: I wish I could say it wasn't relevant because I'm ashamed that it is relevant. Those cigarettes were tested in Japan among females, and they were sent back to Richmond, Virginia to a center called the Product Evaluation Research Center, the PED Center, Product Evaluation Division. I'm sure you know it well, and I'm sure you supplied all the documents about the research the Product Evaluation Division does to the FDA. And I think the FDA should be very thankful to you for submitting those documents. But I'm ashamed because those products were made by a U.S. company. They were tested in Japan and brought back.

Now, more recently, there's been a split by the manufacturers, but this data reflects what was done by a United States company. And I think

whether the research is done in a foreign country or not is irrelevant. We do research in Poland on bladder cancer all the time through NCI funding to better understand bladder cancer. So even if BAT was doing this, it still provides us scientific insight into one, the behavior of the industry, two, the effect of your products, and, three, its impact on initiation.

I think of all the things you people are talking about, the most important thing is initiation; deny the ability to create a new generation of smokers. Give the industry all the current smokers. Let the lawyers and let all the cessation people fight over the current smokers; but deny the opportunity to create new smokers through your scientific knowledge and through your moral courage.

DR. SAMET: Any other questions?

[No response.]

DR. SAMET: Just two comments, one just to put the Japanese story in context, at this point, the Japan tobacco is still 67 percent owned by the

government, by law.

Second point, I think, for our committee, what we should be looking at here very carefully, is what we can learn about marketing and initiation and then lessons that may be extended. And I think we'll take a close look at that with understanding the generalizability issues.

Are there other questions for Greg?

[No response.]

DR. SAMET: Okay, good. Thank you very much.

DR. CONNOLLY: Thank you, and I will return.

DR. SAMET: Thank you.

Our next presentation is by William True from Lorillard. Dr. True?

DR. TRUE: Good afternoon. My name is Bill True, the senior vice-president of Research and Development at Lorillard Tobacco Company, and I appreciate the opportunity to provide these comments with you today.

As a reminder, the congressional mandate given to FDA and to TPSAC was to consider the

impact of the use of menthol cigarettes on public health, and address the countervailing effects of any menthol recommendations, such as the creation of a black market in menthol cigarettes. Stepping back from the year-long process, we believe the evidence shows there is no justification for increased regulation of menthol cigarettes.

Let's start with the science. The overwhelming body of scientific evidence, whether epidemiology, biomarkers, toxicity, chemistry, or smoking topography, all show that menthol and non-menthol cigarettes are equally dangerous.

I would also like to address the question of whether menthol has a disproportionate effect on African-Americans, one of the groups identified specifically by FDA. Epidemiology studies show no difference in lung cancer and other smoking-related disease risks between all menthol and non-menthol smokers. This also holds true when we focus specifically on the African-American population, who primarily smoke menthol.

The studies on the slide represent all of

the primary epidemiology studies that compare the lung cancer risks of African-American menthol and non-menthol smokers. The data clearly show no significant difference in lung cancer risks. In fact, several of these studies report that lung cancer risk ratios for African-American menthol smokers are slightly lower than African-American non-menthol smokers.

Notably, the Etzel study, which included only African-Americans, found near-significant reduced risk for current menthol smokers. The authors concluded that quote, "Our data suggested a possible protective effect of mentholated cigarettes for current smokers," unquote.

Epidemiology and other smoking-related diseases also show similar risk for African-American menthol and non-menthol smokers. Looking at the African-American demographic provides additional insights beyond the impact of disease. That's because, while nearly 2 times the number of white menthol smokers than African-American smokers, 82 percent of African-American smokers

smoke menthol. There is no better population group to look at to measure the effects of menthol. And as I said earlier, menthol smokers in this group have no higher incidence of lung cancer or other diseases.

According to recent data, African-Americans also have a slightly lower overall smoking rate than do whites, 76 percent of whom smoke non-menthol cigarettes. Further, African-American menthol smokers begin smoking later in life than white smokers and have a much lower youth smoking rate, about half.

To reiterate, the smoking population demographic, which has a strong and historic preference for menthol, does not have a higher smoking rate, does not smoke more, does not get more disease, starts smoking later in life, and has half the youth usage. If menthol cigarettes had a negative impact on public health, you would surely see it in this population, and you don't.

I would also like to address menthol in youth smoking. The question of the impact of the

existence or prevalence of menthol cigarettes on youth smoking and usage rates can best be evaluated by studying examples that naturally exist in the U.S. and around the world.

As we have presented before, when you look at the menthol market share and youth smoking prevalence on a state-by-state basis, youth usage is lowest in high-menthol market share states. There is simply no evidence that youth smoking rates in the U.S. would decline if menthol cigarettes were not available. In fact, this is also true on a global basis. This slide represents data on menthol market share in various countries, represented by the green line, and the adult and youth smoking rates in those countries.

In many countries, the share of menthol is very low, and in some, menthol cigarettes are effectively unavailable. Many of these countries continue to have adult and youth smoking rates that are higher than those in the U.S. So as you can see, there is simply no relationship between menthol share and youth usage or smoking incidence

globally.

While NSDUH and other national surveys provide some meaningful data, conclusions about smoking initiation cannot be drawn from these surveys because they do not include a question about menthol use at smoking initiation. We must be mindful of the limitations on the conclusions that can be drawn about youth preference for menthol cigarettes from NSDUH data because of the potential for misclassification of menthol use, as well as the small sample sizes in the youngest age categories.

NSDUH's findings may plausibly infer some experimentation by youth with menthol cigarettes, but other data show that only one in four youthful experimenters go onto become regular smokers. Therefore, any inference drawn from NSDUH about any effect of menthol on initiation of regular smoking must consider these limitations.

While scientific proof of a disproportional impact of menthol on public health does not exist, the countervailing effects, like black markets and

increased crime, are real and proven, as you have seen presented to you many times.

Cigarettes are a hazardous product. It is plausible that restrictions on any market segment involving a hazardous product would result in some public health benefit because a number of users might quit using the product as a result of those restrictions.

This slide shows one way to view current cigarette market segments. You could impose restrictions on any taste preference segment in the market, whether that be menthol, non-menthol, lower tar, higher tar, filtered, or non-filtered cigarettes, and have some impact on quitting. But that is a very different question than whether that same segment has a unique and disproportionate impact on public health.

So, in conclusion, we urge you in your report writing to remember that you were given a clear congressional and FDA mandate to follow the signs. The use of menthol in cigarettes does not disproportionate impact public health.

The overwhelming scientific and real-world market data demonstrates there is no difference in disease, initiation, cessation, or dependence between menthol and non-menthol cigarettes. And, finally, keep in mind that Congress's purpose of granting FDA with the authority to regulate tobacco was to create order and supervision of the industry, not create chaos, the likes of which we have not seen since prohibition. Thank you.

DR. SAMET: Okay. Thank you. Questions? Mark?

DR. CLANTON: Just a couple of questions, because I think there was some confusion there. First, some data about comparing African-American lung cancer rates who smoke menthol versus non-menthol, and saying there was no difference. But then I also heard maybe some slips, talking about there's no increased disease burden among African-Americans who smoke.

I'm not sure the data shows that, but here's my question. My first question is, do you agree that smoking increases the risk of developing lung

cancer?

DR. TRUE: Smoking any cigarette increases the risk of developing lung cancer.

DR. CLANTON: Would you also agree that anything that causes an African-American to smoke would consequently and subsequently increase his or her risk of developing lung cancer?

DR. TRUE: I think every individual has a choice of the product that they would choose to smoke, whether that be non-menthol, whether that be menthol, whether it be a tar category, or any other configuration.

DR. CLANTON: I'll take that as non-responsive.

DR. SAMET: Other questions?

[No response.]

DR. SAMET: Okay. Thank you for your presentation.

Next, we'll move to Jim Tozzi from the Center for Regulatory Effectiveness.

MR. TOZZI: Good afternoon. I'm Jim Tozzi. I'm with the Center for Regulatory Effectiveness.

We're regulatory watchdogs that enforce or look at agency compliance with the good government statutes, and you know the good government statutes include the Data Quality Act, Paperwork Reduction Act, Regulatory Flexibility Act, and a number of other activities. And we report on those mechanisms.

We are funded and get grants from virtually every industrial sector, including the tobacco industry. I have one comment on one report that I wanted to call to your attention, but prior to doing that, I'd like to make two other statements.

First, I would like to compliment TPSAC for the very transparent process that you are engaging in, and I'm even more appreciative of the fact that TPSAC is writing a report on its own and only by TPSAC, which I think stands very highly for the committee. And, lastly, I think I'd also like to compliment FDA. Having served on a number of advisory committees, it's pathbreaking work. You let the public see drafts of the report before they go out, and you're to be applauded for that.

I have one comment on one of the studies that were issued or commented on in the last session, and it had to do with the NCI study. And the NCI study of the last session, if you recall, was tied to what menthol smokers report they would do if menthol cigarettes were no longer sold. And the report had two conclusions, which were discussed much.

One said that 39 percent of menthol smokers say they would quit all tobacco use if menthol cigarettes were no longer sold, and the second said behavioral intention is associated with actual behavior.

Allow me to comment on those two findings. It's well that the author concluded that 39 percent of menthol smokers said they would quit, but the reverse side of that question is, at what percentage of menthol smokers would quit in the absence of a ban? If there was no ban under consideration, what is the statistic? And I think that's a relevant statistic.

What we did, we went into the data supported

by NCI that NCI quoted – and it's a secondary analysis, and all you all know as good as I, secondary analyses are right on point, but you have to pull down. But other people did it, and Trinidad, and his colleagues did it. And they came up with the conclusion that 44 percent of current menthol smokers report that they would quit within six months.

Then you want to ask, what about subpopulations of interest, African-Americans? And Unger -- and really their colleagues also quoted him, one of the FDA studies -- came up with 46 percent.

The point that I'm making, the data suggests whether a ban is under consideration or not, the intention to quit ratios that are within the noise level are about the same. So I take exception with that NCI report that just includes that one piece of data.

Now, let us go to the other statement they had, and that had to do with behavioral intention is associated with actual behavior. This is a very

unusual discipline if you're going to start looking at psychological studies, and we have not looked at those into detail. We have done other studies.

But I will say that we looked a couple of the most definitive studies, and one of the more specific ones quoted in the literature goes back to Wicker. And he says -- you know, this all is an outgrowth of the following. He says, "The spontaneous confidence that verbal behavior on surveys," applies to a lot of the data before this committee, "very frequently predicts action in real life, is that as children, we are given careful training and truthful behavior. We are impressed with social importance and keeping promises, whether or not we do so."

So what I'm suggesting is there's a lot of literature that really takes exception with that statement by NCI. And, finally, if you really like nerdy studies, there's one by Armitage & Conner, which is unbelievable. It went through 183 psychological studies of behavior, what they call the intention behavioral gap, and they did a meta-

analysis of them, and they looked at all the details. And we're going to be posting my comments up on our website in the next 24 hours, I hope. And he concluded that behavioral intentions failed to explain over 70 percent of the variance in behavior.

So where does this leave me? The NCI, very, very prestigious institution, and one that I worked with for a number of years, I think the study, standing alone, without additional analyses like I suggest, gives somewhat of an incomplete picture. And I would beg the committee, as a role of governance, that people know agencies, that when they come to TPSAC, they are held to the same accountable standard that they do when they go to the White House to support a budget or legislation. They have to have complete data and give you both sides. And I think that data was right, but I don't think it was complete.

So where I come out on this, I think that standing alone, that study's not ready for primetime. Thank you.

DR. SAMET: Thank you, and thank you for the compliments. We'll take them when we can get them.

MR. TOZZI: Not very often.

DR. SAMET: Let's see. Questions?

[No response.]

DR. SAMET: Okay. Thank you.

We'll move to our next presentation, Mohamadi Sarkar from Altria.

DR. SARKAR: Good afternoon. My name is Mohamadi Sarkar. I am from Altria Client Services, and I'm speaking here on behalf of Philip Morris, USA. I'm here to respond to some of the questions that have been raised by the committee members regarding comparisons made between adult menthol and non-menthol smokers from the total exposure study.

Here is an outline of my presentation. After a brief background, I'd like to show you results of some additional analysis that was done to address the questions raised. And based on this analysis, we were able to conclude that exposure and dependence measures were not higher in the

menthol smokers compared to non-menthol smokers in the subgroup that smoked 10 or fewer cigarettes per day.

This slide summarizes the various submissions and presentations that we have made, along with the entire TES data set that was submitted, the raw data, as well as the underlying documentation. I don't believe that the previous presentation did enough justice to cover the comprehensive analysis and the submissions that were made to address all the issues that are on the table on menthol.

So before I show you the results, let me just quickly go through the study design. The total exposure study was a cross-sectional study in a large number of adult smokers and non-smokers across multiple sites in many different states in the country.

This slide lists the primary and the secondary objectives of the study, which I had described in detail during my July presentation. And this slide shows as a recap of the key summary

points that I made during my July presentation.

There are four key points that I want you to remember. The first one was that, based on the analysis that we did for all the smokers, there were no differences between menthol and non-menthol smokers. The other point that we made was that, based on the metabolite ratio, menthol did not appear to inhibit the metabolism of nicotine or NNK. And I know there were some discussions during the January meeting around this issue, and I just wanted to remind the committee that we presented some very compelling evidence, indicating that this was not the case.

The third point was that there were no significant differences in the biomarkers of potential harm, and the fourth point was that menthol smokers did not have higher FTND scores compared to non-menthol smokers.

This slide is a summary of some of the questions that have been raised, both during the July meeting, as well as during the January meeting. Due to the time constraints, I can't go

through the details, but the overall theme of the questions led us to do this additional analysis with the objective of determining whether there were any differences in both the exposure measures and dependence measures in this subgroup that smoked 10 or fewer cigarettes per day.

So since the discussion has been around the relationship with numbers of cigarettes, I thought it would be worthwhile to just look at this. In this case, I'm showing you one of the biomarkers of exposure, serum cotinine, against number of cigarettes. And you're looking at the data for about 1,000 menthol smokers and 2,000 non-menthol smokers. While, generally, the relationship tends to be linear, there is a lot of variability, but the slopes of the two relationships are very similar. And what I'm going to do today is just show you data from a very small subset of this population.

So the demographics of this subset is shown on this slide. The sample size is shown at the top. And I just wanted you to note a few things.

The number of cigarettes smoked was similar between the two -- it was about 7 cigarettes per day -- but there were some inherent differences between the two groups. Note that the tar yield of the menthol smokers tends to be higher. The BMI is slightly higher, but most importantly, the race distribution is different between the two groups. There's a larger proportion of African-Americans, as we have seen from all the literature. I want to remind the committee that I showed in July, when you look at the overall population of smokers, whites are the majority menthol smokers.

In this slide, I am showing you the results from the analysis of the biomarkers of exposure that we investigated. You're looking at menthol and non-menthol smokers, the unadjusted mean, and the standard deviation for each of these groups. And as I said earlier, since there were inherent differences between the two groups, we did a statistical analysis based on an analysis of covariance model. And based on this model, these biomarkers of exposure were not significantly

higher in menthol smokers compared to non-menthol smokers.

Due to the interest in the racial subgroups, we also looked at the white menthol, non-menthol, and African-American menthol, non-menthol smokers, and, once again, based on the statistical model, the menthol smokers did not have higher biomarkers of exposure than non-menthol smokers.

I do want to point out that the serum cotinine levels for both menthol and non-menthol smokers in the African-American subgroup was higher, presumably due to the metabolic differences that I'd shown in the July presentation.

This slide lists the analysis for the Fagerstrom test for nicotine dependence in this subgroup. And based on the logistic regression analysis that we did, no significant effect of menthol was observed in this score, regardless of how the scores were categorized.

The next slide is a analysis of the time to first cigarette from the Fagerstrom test. And when we do the logistic regression, we found that this

particular dependence measure, the odds of smoking within five minutes of waking were not statistically significantly higher in the menthol smokers compared to non-menthol smokers.

That leads us to the conclusion that, based on the analysis in this subgroup, both the exposure and dependence measures were not significantly higher in menthol compared to non-menthol smokers. And these results, overall, are very much consistent with the July presentation, where we looked at all the adult smokers. And I want to end the talk by reiterating that the results of this analysis adds to the existing body of evidence that menthol does not seem to effect exposure and dependence measures, and thank you for your attention.

DR. SAMET: Okay. Thank you.

Questions? Jack?

DR. HENNINGFIELD: Just a couple. I was trying to keep up with the math, but what was the average age of onset of the smokers in the two groups? It looked like it was 22.

DR. SARKAR: In the total exposure study, we had recruited only age-verified 21 and older, so that age that I showed you was the average age of this population. We didn't look at the age of onset.

DR. HENNINGFIELD: But if I subtract their age from years smoking, it looks like about 22 years and 22 years?

DR. SARKAR: I'd be a bit careful because what you're looking at is the average of the population and then the average of the number of years smoking.

DR. HENNINGFIELD: But my question is, is the average age of onset of smoking, or is there something funny about the math, about 22 years? Based on that, it is, right? No?

DR. SARKAR: What I am saying is that what you're looking at is the average age of that population, and then the average age of years of smoking. So I'd be careful drawing -- interpretations.

DR. HENNINGFIELD: So if the average age is

38 years, and that group has been smoking an average of 16 years, then their average age of onset was 22, about the same as true of the other column. So if it's anything close to that, this is a really weird population. It's not representative. So that's one observation or question.

The second is, adults 38 years old that have been smoking for 16, 17 years, that are smoking fewer than 10 cigarettes per day, are also not a U.S. population, representative population. That doesn't make sense.

So you're making generalizations based on a weird population. That's my technical term.

DR. SARKAR: Let me just inform the committee that this particular analysis was specifically done to address the questions that have been raised by the committee members, to look at a subgroup. This was not intended to be the representative of the entire smoking population.

DR. HENNINGFIELD: I think that's part of my point.

DR. SARKAR: Yes. So in July I showed you the data.

DR. SAMET: Let me raise a question about all this science here. First, we appreciate you bringing in these analyses forward to us. I guess my concern, really, you have the data you have, and the principal issue in my mind is actually that you've sort of pushed the idea of statistical adjustment to beyond its limits. And with the racial imbalance, in fact, I'm not sure what, quote, "adjusting for race," means in practice. I recognize that you can put an indicator variable into a regression model, but that is quite different from interpretation.

The ideal sample here would be a group of individuals within either racial group, but stratified by race, who smoke less than 10 cigarettes a day and in equal or approximately balanced numbers, smokers of menthol to non-menthol cigarettes.

You clearly have substantial imbalance. And I think in the face of that, you just have to be

quite guarded in the interpretation of the findings. And, unfortunately, if you were to stratify, which I think probably is a reasonable thing to do -- I mean, in fact, within the whites, the numbers are not unreasonable -- you should probably do those analyses stratified by racial group and set aside the, quote, "adjusted model," because I think its interpretation is not particularly clear to me. And, in fact, the simple indicator variable that you probably used probably does not, in fact, represent the actual relationships here.

So if we have a chance to see you again, and you were to present, I think the stratified analysis would probably be more informative, so no need to respond.

Let's see. Neal?

DR. BENOWITZ: First, I'd like to thank you for bringing this in. I think it's very important to look at these data. It's been shown by a number of groups that the fewer cigarettes you smoke per day on average, the more you take in per cigarette,

of all kinds of stuff, of nicotine, of NNAL, or NNK, of everything.

So if you were to plot cigarettes per day versus intake per cigarette, you would see a negative slope. That's been shown by many people. It's also been shown by Muscat that dependence affects that slope, so that the more dependent you are, the steeper that slope is.

It would be informative to go back and look at this, specifically looking at the cigarettes per day or maybe groups of two cigarettes per day, and look at that within race groups, and look and see if that slope of biomarker per cigarette per day -- first if cigarettes per day in this 10-and-under group is different, because that would really address the concern in my head.

When people are really smoking very few cigarettes per day, like a lot of African-Americans do, that they're taking huge puffs, and therefore, they're able to take in much more nicotine and much more carcinogens because of the facilitating effect of menthol. So that's the question I'd like to see

addressed.

DR. SARKAR: A few points that I'd like to make, to address some of the questions that you raised. First of all, I think we have to be mindful of the fact that when you look at the adjusted biomarkers, biomarkers adjusted by number of cigarettes, that data is only good as how accurately you have gathered the information about the number of cigarettes that they smoke. And then, overall, as you're trying to understand the impact on the biological effect of exposure, I would hope that you'd agree that the daily exposure is probably better represented of the overall impact. And I've read as well that there's this perception that African-Americans smoke fewer cigarettes, and, therefore, somehow, they get more out of a cigarette.

I'm not sure on the data here, but we have done an exhaustive submission, both during the written submission in March and in July, and I came into this presentation, and you have the entire TES data set, and I'm sure if there was some specific

analysis that could be done and had to be done -- but we looked at the topography data. And when you look at the topography, being mindful that topography has its own limitations because you have the device that can interject, you don't see any differences.

So I'm convinced, at least based on the total exposure study data. And, remember, this is a very, very large data set, which has been very systematically characterized across all the biomarkers, and we have looked at a number of different variables. I am not convinced that there is any difference in exposure or the dependence measures between these two groups, regardless of whether you look at the entire population or within the small subset of 10 or fewer cigarettes per day.

DR. SAMET: This is a comment, and I've made this comment. I'm just going to offer a reminder. I think that since FDA does have the data set, I think the question of whether additional analyses could be done on a time frame that would be of value, I think, is a question. And I know that

your sort of analytic capabilities probably are now quite busy, for example, some of the kinds of analyses that Neal mentioned or I mentioned. I know it takes a while to get up to speed with a large data set.

Who am I looking at? Corinne? I'm looking at both of you and asking about the capability, if we were to direct some analysis requests at you, would you be able to get them done? And I guess the question is, have you gained some familiarity with this database, and can sort of get things done easily?

DR. ASHLEY: On the time frame that you will need the data, it's going to be very hard.

DR. SAMET: You mean by tomorrow?

[Laughter.]

DR. SAMET: That is the question.

Okay. Mark?

DR. CLANTON: I want to ask the question that Neal asked in a much more simple way. And it's back to this issue of number of cigarettes smoked per day by African-Americans as that plays

into the measure of addiction, the Fagerstrom test.

So would you agree that the Fagerstrom test does include number of cigarettes as part of the calculation of addiction?

DR. SARKAR: Yes. It is a component in the FTND score.

DR. CLANTON: It is a component.

DR. SARKAR: Yes.

DR. CLANTON: And do you agree, because you reported, that African-Americans smoke fewer cigarettes per day; correct?

DR. SARKAR: Right.

DR. CLANTON: So in order for there to be roughly the same or no difference in a measure of addiction between these groups, African-Americans, who smoke fewer cigarettes per day but have roughly the same measure of addiction, would actually have to demonstrate some higher level of addiction as a proportion of fewer cigarettes smoked per day; correct?

DR. SARKAR: The presentation that was made earlier had the raw data, and we understand some of

the complexities in trying to interpret just the raw and adjusted mean. But if you'd remember, when the presentation was made earlier, they had looked at -- they had shown the data that we had analyzed. And just looking at the raw data, the numbers are actually lower; in fact, the FTND scores are lower.

So that's built into when you look at the FTND score, because they smoke fewer cigarettes, numbers are lower, in menthol smokers compared to non-menthol smokers.

DR. CLANTON: So the no statistically different is actually lower, you're saying?

DR. SARKAR: That's why, when we looked at the logistic regression, this slide is not necessarily representative of what was shown earlier. But when we showed you the data in July, we did the logistic regression, adjusting for age, race, gender, and number of cigarettes -- I mean, age, race and gender and socioeconomic status, and that's when we showed that there was no significant difference.

DR. CLANTON: Thank you. But again, to

Dr. Samet's point, if you're looking at African-Americans, you can't adjust for race.

DR. SAMET: Jack?

DR. HENNINGFIELD: There is all kinds of analyses that you could to that are theoretically interesting, but this population is so non-representative that I don't know what the value is. When most people in America start smoking in their teens, the average age is 14, 15, everything we know about age of onset is that earlier age of onset is associated with less disease, lower dependence levels. Twenty-two is an old age to be starting. And in terms of the dependence measures, I'm not sure if you're aware of how to score the Fagerstrom, but if all these people are below 10, they're in the lowest categories anyway.

So, again, this is a weird population. It's not representative, so I don't know what the value is, other than – there are always scientific questions that are interesting, but in terms of addressing our questions, I don't know why you'd bother.

DR. SARKAR: I would respectfully disagree with you. I think this study was designed to be representative, and you can see from the map that this is a sampling of a large number of adult smokers and non-smokers from the country.

DR. HENNINGFIELD: In all of those places, the average age of onset is someplace between 14 and 16, and they're smoking closer to 15 cigarettes per day or more.

DR. SARKAR: A few things that we have to remember, that this study was done to recruit smokers 21 years and older.

DR. HENNINGFIELD: That's fine; so it's limited.

DR. SAMET: Actually, just to go back to Jack's point, I think the first order of issue is actually whether the relationships observed within the study are valid or not, and then the question of generalizing them becomes the second. I think on the Fagerstrom score, by restricting the range of number of cigarettes smoked, you've actually restricted the range of the score. And then I

think it becomes more difficult to observe a difference. So that it might be better to look at the more or most powerful predictor, which is time after getting up to first cigarette, for example, and set aside the full score, because I think, you've, in a sense, lost its validity as a measure by restricting the range.

But I think let's not discuss the details of future analyses here. And I recognize it was a very large data set. You could speak on it forever.

DR. SARKAR: Can I just make one last point? Yes. Actually, this analysis was done specifically to respond to the questions. And we have shown the entire data set, and during that time, we had pulled out the time to first cigarette and analyzed that, and the data was shown during the July presentation.

DR. SAMET: Memory has failed since July.

DR. SARKAR: I would urge you to go back to the July presentation.

DR. SAMET: Thank you. I will. Thank you

very much for your presentation.

Next, we'll move onto Edgar Adams from Covance Market Access Services, Inc.

DR. ADAMS: Thank you. This study was funded by Lorillard Tobacco Company, and it was a review of the literature. By way of introduction, obviously, I'm Edgar Adams. I'm the executive director for epidemiology at Covance and former director of the Division of Epidemiology and Prevention Research at NIDA.

My coworkers on this were Dr. Emily Durden and Felicia Bergstrom. This was originally going to be an 11-minute presentation, but, unfortunately, Felicia broke her arm in three places and cannot be here today. So I'm not going to go over all the slides. This was developed as an 11-minute presentation, so I'm going to cut out a bunch of the slides. I'm just going to go through them.

I should also note that what you see here is my presentation. Even my coworkers did not, basically, approve this presentation. I worked it

out with one of them, but what you see here is my presentation. And when I went through it, in a sense, I asked the question, if I had to make a recommendation based on the data that are available, could I make that recommendation?

I actually had to address this issue more than 20 years ago when I was on the committee that had to make a recommendation in regard to the scheduling of steroids. And the data at that time did not support scheduling of steroids. It did not meet the criteria for the A factor analysis, and we had many months of discussions on that issue, as you might imagine.

So our premise was, the science-based recommendation must be -- the data must be, sufficient quality to support and defend the recommendation. And we reviewed the published literature, and also the contents of the surveys, which I am not going to discuss.

We essentially started with 473 articles in the literature search, including the NCI bibliography plus others, and ended up agreeing

that we needed to review and evaluate 28 of those articles. We did a subsequent review on an additional 24, and picked 10 of those articles for further review and evaluation. So at the end of the day, we reviewed 38 articles.

You all have the report that we submitted, so you can see the criteria. In essence, we did the review using the AHRQ criteria that they used in the 2006 report, and we used the same ratings of good to poor for the overall quality. And then we did separate ratings in terms of the quality for making inferences on menthol.

In essence, we found that the studies were generally well-designed, but often poorly designed to analyze the effect of menthol on the behaviors of interest, which as it turns out, is consistent, if you've already read the Foltz (ph) article and the recent supplement; in essence, he came to the same conclusion.

We rated 26 of the 38 articles fair or better. And as did AHRQ, we looked at those that were rated fair or better. We then looked at 15

studies of that 26 for their ability to look at inference on menthol.

Considering an additional 15 studies, we focused on whether the authors presented conclusions regarding the impact of menthol on smoking behavior, whether the author's conclusions were supported by the study findings, and whether the author's considered conclusions reflected the totality of the findings.

What do I mean by that? One of the studies, Okeyumi (ph), is often cited, and he cites a difference at six weeks, which is apparently actually seven weeks, but no differences at six months with the whole study concentrating on the six-week finding rather than the six-month finding.

So that was an example where we believe that the study did not reflect the totality of the findings. There was one or two other studies where a conclusion was drawn, and then in the discussion, it mentioned -- or maybe even in the same paragraph, it mentioned that while they drew this conclusion, the differences were not statistically

significant.

So taking the 38 studies and the 15 that were good or fair, we ended up saying that six made appropriate inferences and -- I'm sorry. Seven made appropriate inferences and the others did not. And of those, there was no difference between menthol and non-menthol in five of the studies, and a difference in one of the studies. And, frankly, if you looked at the other studies that we felt didn't make appropriate inferences, it was about 50/50 or maybe 60/40 in terms of no difference.

I'm not going to go through the surveys, as I've already mentioned. These are the surveys that are often used, and a lot of the reports are based on these surveys. But in the interest of my remaining 59 seconds, let me just go to the conclusions.

So the question was, did menthol flavoring differentially affect smoking behavior compared to non-menthol, and to what extent? And, again, the premise that we began with was, does the data have sufficient quality to support and defend a policy

recommendation? And as I noted earlier, from a personal standpoint, having experienced this issue, I asked myself, if I had to make a recommendation based on these data alone, would I feel comfortable doing that?

The answer is, the data are mixed, so I would personally have a difficult time making a recommendation solely on the data. I know there's been larger public health issues raised, and some social justice issues raised. Those are different issues independent of the data, and thank you for your time.

DR. SAMET: Thank you for your presentation. Let me ask one question. I read your report with interesting, at least as I understood what you did. You evaluated each of the studies individually, using your rating approach, but you did not make an attempt to synthesize the evidence. You only evaluated the individual studies and gave your evaluations for them. And that is, there was nothing constructive about the effort. It was really looking at the studies one by one, and then

doing what you called a quality evaluation.

At the end, yet you offered some overall overriding concerns. And were those reached on the basis of the review that you did or were those reached on some other basis?

DR. ADAMS: Let me back up one second. One of the things that we did was, we had two reviewers read each study and then rate them independently. And if we agreed, that was fine; if we disagreed, we had a discussion. And then if we couldn't agree, we had a third reviewer review the study.

Essentially, the conclusion is based on the fact that the data were quite mixed. Many of the studies were not designed to address the menthol question, as is discussed in the supplement that came out in December. Studies that were there that seemed to be of pretty good quality are mixed. The majority of the ones that we thought were the best studies suggest that there's no difference between the two.

So that's the sense of what the recommendation is based on. The recommendation is,

this is going to be difficult to do based solely on the data unless more data becomes available.

DR. SAMET: Okay. I think I will just comment --

DR. ADAMS: Did I not answer your question?

DR. SAMET: I think you satisfactorily summarized what you did. I think it's what you didn't do that I was pointing to. And, of course, judgments often have to be made in the face of incomplete, and quote, "mixed," evidence. And we are grappling with that. I think, again, just as an important point for those who are listening, we obviously are looking carefully at the quality of all evidence that we consider. And we certainly appreciate the efforts of others to evaluate and compile these studies as well, and we're happy to have people contribute to getting our work done.

Let's see if there are others. Patricia?

DR. HENDERSON: I realize this is a industry-funded study. Had the results been different, would you have still presented your data?

DR. ADAMS: The industry had no input into the presentation whatsoever, and the answer to the question is yes. When we agreed to do this study, it was purely, from a scientific objective, look at the data. And it was part of our contract that they would have no input into the results or what we did with the results.

DR. SAMET: Okay. Other questions?

[No response.]

DR. SAMET: Okay. Thank you.

We'll move to, now, Joe Murillo from Altria.

MR. MURILLO: Mr. Chairman, thank you for the opportunity to address the committee. My name is Joe Murillo. I am vice-president and associate general counsel for Altria Client Services. I'm here today on behalf of Philip Morris, USA. As part of my job, I oversee our brand integrity department, which we formed nearly 10 years ago to lead the company's efforts to combat illicit trade.

We undertook that effort, because as tobacco products move outside of the legal distribution chain, law-abiding businesses lose revenue,

consumers lose out on quality, and states and locality lose taxes while experiencing higher levels of crime. That is why we have developed a strategy shown on this slide.

Our efforts range from monitoring sales channels for illicit activity to advocating for legislation that strengthens the law in this area. In addition, we have supported hundreds of law enforcement investigations. This includes working with the ATF, the TTB, the FBI, and dozens of other federal, state, and local law enforcement agencies. We've also brought lawsuits against thousands of entities to stop counterfeiting and other contraband activity. I'd like to talk to you today about the countervailing effects of a possible ban or significant restriction on menthol.

We discussed these effects in detail in our December 30th submission to the FDA. They include a significant expansion of the unregulated illicit trade, increases in organized crime, increased burdens on law enforcement, an erosion of efforts to prevent underage access, declining tax revenues

and payments to the states, significant job losses, and increased self-mentholation of cigarettes.

My remarks today will focus on the illicit cigarette trade. Based on our years of experience in this area, we believe that a ban or other restriction on menthol would result in a significant increase in the demand for contraband cigarettes. While the exact amount of this increase may be the subject of debate, there is little doubt that a large increase would occur.

We expect that existing criminal networks will adapt and expand to supply contraband menthol cigarettes to fill the unmet demand that a ban would cause. There would likely be three sources of illicit menthol cigarettes in case of a ban; first, unlicensed and unregulated manufacturers; smugglers who illegally import cigarettes meant for sale outside the United States; and, finally, counterfeiters.

Regarding the first group, a number of unlicensed and unregulated cigarette manufacturers currently operate in North America. Some of these

manufacturers are reportedly on Native American reservations along the U.S./Canadian border. According to government reports, these manufacturers produce millions of unregulated cigarettes every day.

The cigarettes they produce, which include menthol varieties, are often sold in plastic bags, and are called loosies. Examples of loosies seized by the ATF and the Canada Border Services Agency are shown on this slide.

Loosies demonstrate the remarkable capacity of illicit cigarette traders to fill a demand where legitimate products are either too expensive or not available. It is estimated that these untaxed, unlabeled, and unregulated loosies account for 40 to 50 percent of all cigarettes smoked in certain areas of Canada.

Illegally imported cigarettes are another form of illicit trade. This slide, for example, shows the front and back of Marlboro menthol cigarettes that were manufactured by Philip Morris International for sale in the Philippines. Philip

Morris International is a separate company operating outside of the United States. These cigarettes were illegally diverted by smugglers and were seized by U.S. customs en route to Illinois.

We're also greatly concerned about an increase in counterfeit cigarettes. Counterfeit cigarettes are fakes, designed to look like the real thing. The Marlboro menthol cigarettes pictured on the left of the slide are counterfeits recently intercepted by U.S. customs in Chicago. The pack of Newports pictured on the right was purchased through a website and shipped from China.

It is hard to appreciate from just these pictures how similar in appearance these packs are to genuine packaging. Counterfeiters have developed sophisticated methods of producing high-quality packaging, and it usually takes an industry expert to tell the difference.

The majority of counterfeit cigarettes sold in the United States originate from China. Counterfeiters in China are reported to have the capacity to produce more than 400 billion

counterfeit cigarettes per year. To put that in perspective, that would account for 125 percent of the U.S. total cigarette volume.

Now, genuine cigarettes sold by PM USA are manufactured in modern, regulated facilities such as these, which is registered with and subject to inspection by the FDA. By contrast, facilities used to produce counterfeit cigarettes, such as these in China, do not operate under the same product regulation or controls.

Illicit cigarettes are distributed in a variety of ways. Counterfeit and illegal imports often arrive in large container shipments. Unlicensed domestic manufacturers ship by the truckload. These products are then often distributed through organized criminal networks, to retail shops, and vendors on the street. But one of the most alarming distribution channels is the simple point-and-click order through the Internet.

As this slide indicates, a recent Google search for cheap menthol cigarettes produced about 290,000 hits. As an example of what these sites

offer, this slide shows screenshots of websites that sell untaxed, unregulated, counterfeit, and other illicit cigarettes to U.S. consumers. The cigarettes offered for sale include menthol variants of U.S. and international brands, many of them complete with counterfeit state tax stamps. These websites are readily available to U.S. consumers and offer express shipment into the United States.

Whether through the Internet or through other means of distribution, illicit sales often involve large organized crime. It has been widely reported that major international criminal organizations participate in the illicit cigarette trade and use the substantial profits to fund other criminal activities. A menthol ban would likely create more opportunities for a variety of enterprises. We urge the committee and the FDA to carefully consider these likely effects, and I thank you for the opportunity to address you today.

DR. SAMET: Okay. Thank you.

Questions? Mark?

DR. CLANTON: So, basically, we did see some information about counterfeiting and contraband as it relates to regular tobacco. So I'd like to ask you to give your best guess as to what the difference would be between contraband for regular tobacco, which is legal and widely available, and what would the effect of a ban be on menthol cigarettes when it comes to contraband and tobacco?

MR. MURILLO: That's hard to assess. What I'm trying to do is give you perspectives based on our work, and we've cited to a number of pieces of government-collected data, et cetera. What I would tell you is that there is enormous capacity for producing counterfeit cigarettes at factories like the one you saw. Making them into menthol cigarettes is not, seemingly, a barrier. And we know today, in New York State, for example, that about a third of all cigarettes being sold, including the menthol varieties, which are extremely popular in that state, are available on the street through contraband sales.

DR. CLANTON: So one more question. So I

agree with you completely that given that there are issues related to organized crime, and contraband, and counterfeiting just with regular tobacco, it is difficult to understand what the real difference or marginal difference might be when it comes to menthol cigarettes. We already have all of those issues in place.

So my next question has to do with capacity. So, again, one of the pieces of data you presented had to do with unlicensed manufacture of menthol cigarettes. And, again, we were talking -- I think you talked about American Indians and their role in this.

So are you really asserting that there is an equivalent capacity, through either unlicensed manufacture or illegal manufacture, to produce the same number of menthol cigarettes as are currently produced by legal means?

MR. MURILLO: What I would suggest is that when you go back to our report, there is plenty of capacity in China. There is, seemingly, a lot of capacity in these unlicensed manufacturing

facilities on the Canadian border. I think the capacity in China, which is reported not only by a number of watchdog groups, but also through the Chinese government, is staggering. When you think about 125 percent of the entire volume of all cigarettes sold in the United States, I would say that that is tremendous capacity, and that's just for counterfeit cigarettes.

Now, I would go back to your other question. And the other thing that I think would be relevant to consider is that there are 95 billion single stick cigarettes sold in menthol, so it is 28, 27 percent of the market. But you can do math and decide what percentage of that would be subject to contraband. The point is that there is plenty of facility and plenty of demand for it today.

DR. SAMET: Dr. Clark?

DR. CLARK: You showed pictures of the modern domestic manufacturing capability and pictures of the illicit manufacturing capability. Have you done any studies about the content of menthol in any of these contraband cigarettes?

Since they're already so ubiquitous, it ostensibly would be to your advantage to note that the menthol content of domestically appropriately manufactured can be regulated, whereas the menthol in the illicit manufactured would not be regulated.

MR. MURILLO: Exactly. The point is that there is no regulation.

DR. CLARK: But have you done studies of the menthol content?

MR. MURILLO: Have we done studies of the menthol content of counterfeit cigarettes? No.

DR. CLARK: Yes. You have pictures of them, so, obviously, you've acquired them for legal purposes. Can you assist us by saying, yeah, we've looked at the menthol content and instead of 7 percent or 8 percent, it's 15 percent or 2 percent?

MR. MURILLO: No. We do not undertake those studies. We turn the product over on request to the government for those studies. The TTB has a lab, and I would urge you to talk to federal agencies, such as the TTB and ATF, who do undertake

studies of the contents of counterfeit cigarettes.

DR. SAMET: Anything else?

[No response.]

DR. SAMET: Thank you.

Our next presentation is by Glynis Lough from Battelle.

MS. LOUGH: Good afternoon. My name is Glynis Lough. I have no personal financial disclosures. My employer, Battelle Memorial Institute, has a long history of conducting tobacco-related research and surveillance, including work with the FDA, other government agencies, and the tobacco industry.

To better align our work with our mission as a not-for-profit research organization dedicated to solving challenges in public health, Battelle has made a corporate commitment to accept no new contracts from the tobacco industry and to phase out our existing contracts by December 31st, 2011. This commitment has come from Battelle's leadership, including the board of directors, the CEO, and the health and life sciences global

president.

Today's comments address recent Battelle research on menthol in cigarettes. This work has been funded either by our internal research and development program or by government clients, including the CDC.

Obtaining conclusive results from human exposure studies on menthol cigarettes is challenging. The literature cites mixed results in previous menthol studies, largely due to two factors; first, physical and chemical differences among the commercial menthol and non-menthol cigarettes used in testing; and, second, smokers' brand loyalties and reluctance to use unfamiliar brands throughout a study period. Additionally, cigarette smoke is a highly dynamic and reactive mixture, and concentrations of key smoke constituents and toxicity may change as smoke ages.

To overcome these challenges, Battelle has developed a new exposure assessment paradigm. Our approach is based on measuring the increase or boost of selected constituents in the smoke that

subjects inhale and exhale. This non-invasive boost measurement paradigm uses real-time methods to characterize particulate, volatile, and semi-volatile components of the smoke as it is generated and as it is exhaled.

This real-time approach allows rapid, evidence-based assessment of exposure differences. We've proposed this boost measurement paradigm as an objective and reliable surrogate to obtain timely information, comparing exposure and biomarkers of exposure among tobacco products.

The deposition of fine and ultrafine particles in smokers is an essential component of the boost measurement paradigm. Ultrafine particles penetrate deeply into the lungs and are particularly efficient delivery vehicles for semi-volatile carcinogens such as TSNAs and PAHs. Size, mass, and chemical composition of particles in smoke and in exhaled breath are important factors in our boost measurement paradigm.

For gas phase constituents, Battelle has developed a real-time method to characterize select

volatile organic compounds in mainstream smoke and in exhaled breath. We measure VoCs on a puff-by-puff basis, including the carcinogens acetaldehyde, 1,3 butadiene, and acrylonitrile, and the breath biomarkers 2,5 dimethylfuran, and acetonitrile. Our VoC methods provide a real-time measure of a smoker's exposure to these target compounds.

We have applied our boost measurement paradigm in two separate human exposure studies to evaluate exposure differences in commercial menthol and non-menthol cigarettes. Menthol cigarette smoke had a significantly larger mass of smaller particles in both mainstream and sidestream smoke. The observed menthol-related differences in particle mass and size distribution require further study to elucidate potential differences in semi-volatile partitioning and to isolate the effects of menthol.

To isolate the effects of menthol in exposure, it is necessary to compare measurements from cigarettes that differ only in menthol content. Battelle has created research cigarettes

by self-mentholating commercial non-menthol cigarettes. Using direct vapor deposition, we reproducibly created research cigarettes with three different levels of menthol.

For the non-menthol in matching menthol cigarettes, we conducted real-time, puff-by-puff analysis of machine-generated mainstream smoke. Menthol in the mainstream, whole smoke increased linearly with menthol concentration in the cigarette, but other key constituents were not changed. These results demonstrate that our self-mentholation technique does not introduce a bias, but provides test cigarettes with reproducible menthol levels.

Importantly, this study demonstrated the unique ability to measure menthol concentrations in real time, which could provide new data on the uptake, distribution, and decay of menthol in the body. Now that we have validated the self-mentholation technique and real-time measurements of menthol, we are beginning to apply the boost measurement suite of analyses.

Real-time measurements of smoke composition, and biomarkers of exposure and breath made with matched non-menthol and menthol cigarettes will allow us to clearly assess the effects of menthol in exposure. Further study is required to definitively answer whether menthol influences exposure to selected constituents, and thereby influences harm.

Based on our initial findings, we recommend conducting a larger, laboratory-based human exposure crossover study on menthol. The study should use test cigarettes that differ only in menthol content, and should apply the real-time boost measurement paradigm to assess altered exposures due to menthol.

We further recommend that regulatory decision-making regarding assessments of reduced exposure, relative harm, and substantial equivalents should incorporate a range of observations. The suite of measurements should include particle size distribution, mass, and composition, percent deposition of mainstream

smoke, real-time analysis of volatiles in exhaled breath and in mainstream smoke, and finally, evaluation of response to exposures in living systems.

These measurements will provide the evidence base needed to make timely and critical decisions on tobacco products for the protection of public health. Thank you.

DR. SAMET: Thank you. And it sounds like some very exciting things to come, but not between now and March 23rd.

Neal?

DR. BENOWITZ: You talked about one result that was very interesting, about a change in the particulate mass with menthol cigarettes. Could you tell us more about what the study design was, and what you found?

MS. LOUGH: The study designed was -- this work is about to be published. It's in the publication process at the moment. The work was on individuals smoking cigarettes and machines smoking them with topography. And in the mainstream and in

the sidestream smoke, we saw a higher number and mass of ultrafine particles.

DR. BENOWITZ: Do you know what those particles are? Are they menthol-containing particles, or do you have any sense of what's going on?

MS. LOUGH: No. The initial results that we had with the commercial cigarettes, the menthol and non-menthol differences, led us to create the research cigarettes so that we can repeat these tests with menthol as the only variable.

DR. BENOWITZ: Were these sort of strong menthol cigarettes like Kools or were they ventilated, low-yield cigarettes? Can you tell us anything about the kind of cigarettes that you tested?

MS. LOUGH: The cigarettes in the studies were -- actually, I'm not entirely certain which ones they used. I think that they were the subjects' cigarettes that they used. The ones that we mentholated for the next comparison were non-mentholated cigarettes with ventilation similar to

what a usual menthol cigarette has, and we mentholated them at three levels of .16 percent, .32 percent, and 1.1 percent.

DR. BENOWITZ: Just a comment. From what I think I've learned, is that there is no characteristic ventilation of a menthol cigarette. Menthol's adjusted according to the ventilation of the cigarette, and so it's hard to say what's a typical ventilation for a menthol cigarette. So if I understand you right, it's pretty complicated, because a menthol is actually engineered with respect to the ventilation of the cigarette.

MS. LOUGH: Right. So that's why we had to settle on one. So we picked one that was in the middle.

DR. SAMET: Just before we go to the next question, you said you have a paper that will be published shortly, or is this going to be published on a time frame where we could look at it?

MS. LOUGH: Not before March.

DR. SAMET: Thank you.

John?

DR. LAUTERBACH: Dr. Samet, I object to the sort of testimony where people are presenting conclusions, but we have no evidence, raw data are not presented, and we can't see anything. I mean, after the mention of this type of work, and, I believe it was for the November 18th TPSAC meeting, I did contact one of the authors that was mentioned, tried to get more data on these things, particularly on the butadiene measurements, was unable to. Yet, the committee appears to be taking some of these conclusions from Battelle as gospel, when, indeed, we have zero experimental data, zero raw data, or anything like that, to decide whether the experimentation is correct or not.

DR. SAMET: I'm not sure I know what gospel is, John, but you can perhaps explain it. But I don't think I saw anybody do anything but sort of try and understand what had been presented.

Obviously, in this case, the absence of evidence means it won't be considered in our process. And I think this is perhaps a technique that once it emerges, and is better known, and

characterized, maybe perhaps it would be useful for future work.

Corinne, did you have a comment?

DR. HUSTEN: I was just going to comment that in the open public hearing, anyone's allowed to present anything they want to present.

MS. LOUGH: We encourage anyone who will be at SRNT next week, we'll have a number of posters there on this work.

DR. SAMET: Dan?

DR. HECK: I was just going to say, I do think that the purpose-made cigarettes you've described are a step in the right direction, because I know that prior Battelle work I think that was presented at the 2009 SRNT Europe meeting, that purported to show differences in the small particle, I did talk to one of the primary authors subsequently, and his cigarettes employed in the study were two commercial brands, indeed, but very different cigarettes, totally different blends and construction. And I think that the approach that you've described now is a more proper way.

I might also add that this real-time measurement of smoke retention or smoke intake versus outtake smoke, the methods have been often applied for some time in the industry. I'm pretty sure American tobacco has taken it to quite some elegant lengths now, and I'd encourage you to keep up with their work; Altria, I think all of the major companies have done work in this area.

DR. SAMET: Other questions?

[No response.]

Committee Discussion

DR. SAMET: Okay. Thank you.

The open public hearing of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. And, again, let me say thank you to the public commenters.

Now, there's still one item left on our agenda for the day, if I read this right. Originally, we had the presentations by Dr. Hersey,

but we've gone through those. The other was discussion of chapters 1 and 2 of our report.

Now, we've had discussions of those before, and I don't think, actually, we have anything to put up. Everybody has been given the chapters, and I believe they've now been posted for the public, if I'm correct. So chapters 1 and 2 have, in fact, been posted.

Just as a reminder for the committee, these chapters describe what it is we are charged with doing and also our approach to doing our job. We've discussed, along the way, the general approach. We've discussed this sort of figure that ties into, in fact, the model that David Mendez shows us. We've spent substantial time on the criteria for characterizing strength of the evidence, which, as you remember, were based around the concept of equipoise.

So I would also note that the chapters have now been edited, and I think are nearing final form. So the menthol subcommittee, of course, will be meeting tomorrow. But I think this is the

opportunity to have further discussion of these chapters as TPSAC before we bring them to the final format for looking at comments received from the public. So I'm not going to walk us through them again, but I think if there are comments that we need to discuss here, we should do so.

David, that wasn't a question before, was it?

So everybody does have 1 and 2, and if you had to fly here from L.A., you would have had a chance to read them, and a lot of other stuff.

[Laughter.]

DR. SAMET: Dan?

DR. HECK: I had a question. I'm not sure if it's appropriate for today or tomorrow, or for Dr. Husten, or to you, Mr. Chairman. When the FDA excluded the industry representatives from the report writing, we were reminded to offer an industry perspective report.

Am I correct in assuming that that report is due and expected on or before the same due date? And a question, perhaps, for the committee here, is

the committee interested in considering the industry's perspective on these topics? And, if so, how will that perspective be incorporated into the committee's own considerations in developing their own final advisory opinion?

DR. SAMET: Let me comment, and I think, probably Corinne will comment, or somebody from FDA will, because I'll ask them to. One, I think we've certainly received substantial input from the industry through the public comment period, and I will say, though, I seem to have lapsed on the one July presentation on the TES. I found these presentations quite useful to go back to, in terms of the materials that they offer, in trying to understand the industry point of view. And, also, there's a substantial compilation of evidence that has been done.

So I feel like we, through the nature of interactions in the public hearing sessions, have had substantial input, and then have had documents provided to us. And I think, as the subcommittee has been moving forward, we have certainly looked

at those materials. So I think, generically and generally, and I think by the nature of the process and our meetings, we have been receiving industry input.

I think then there's the separate matter of the report that is being developed by the industry members of this committee and how, as you move towards completion of your report and the menthol subcommittee moves towards completion of this report, there might be the opportunity for us to look at that document. Of course, the time window is getting narrower and narrower, which I think is what motivates your question.

So, Corinne, maybe this is the time for you, or whoever you want to point a finger at, to step in?

DR. HUSTEN: It's me. It is due at the same time, so to answer your first question. I think at the last meeting, we did ask you if you wanted to present or discuss anything related to the industry perspective. I believe tomorrow, again, there'll be an opportunity for you, if you would like to

present anything, or discuss it, or give anything. And I may be speaking -- but I'm sure the committee would -- if you have drafts or anything that you want to share, I'm sure the committee would welcome those.

DR. SAMET: Absolutely. And we would welcome seeing the work of our colleagues.

DR. HECK: I'd be glad to do that when possible, but as you can imagine, it's quite a monumental task on our end as well.

DR. SAMET: We are finding it rather easy. I don't know what the –

[Laughter.]

DR. SAMET: But, certainly, maybe March 22nd.

Any other comments with respect to chapters 1 and 2? Again, if committee members have not quite taken a last look at this, we can return, certainly for a few moments tomorrow, to chapters 1 and 2 when we convene as a menthol subcommittee.

Yes?

DR. BENOWITZ: I'll just make a general

comment about the causal inference analogy to smoking and lung cancer. The problem with menthol is that we're looking at something different. It could be, if there's direct toxicity of menthol, that lung cancer analogy could play a role. But we know menthol is doing one thing at lower doses, something else at higher doses. It's interacting with nicotine. There are a lot of advertising things. There are a whole lot of different issues involving menthol that make it different from the usual toxicology evaluation, where you say, does this chemical cause cancer.

It's such a complicated thing, and so I know why the causal link stuff is here, but I think we really need to make it clear that this doesn't exactly fit that model.

DR. SAMET: Maybe it's not clear why it's there because the reason it is there really relates to the idea of a structured interpretation of the strength of evidence. I agree with you that we have multiple outcomes for which we are interested in the associations with menthol, the presence of

menthol in cigarettes or menthol cigarettes, and that in some instances, the concern is not with causation, per se.

Perhaps, we need to make clear -- and I think, again, this is the kind of discussion that I think is very helpful in looking at the text -- this is not a one-to-one analogy. I think what we want to draw out of the extensive work, particularly around tobacco, on classification, strength of evidence, is the idea of graded classification of strength of evidence that certainly figures in elsewhere, and that we are applying those principles broadly to our problem. And then in fact we have come up with the scheme that we proposed that we think is generally applicable to a wide range of questions.

Because you're right. I mean, we're going, for everything, from things like biomarkers, to relative risk of disease, to the consequences of marketing. So I think we probably can take a close look. Those are the kinds of comments I think would be very helpful in bringing this to a close,

so we've got one already, and he's in San Francisco; note.

Other comments? We can return to this in the morning.

Mark?

DR. CLANTON: Before I ask this, I want to ask permission. May I ask a question that's not related to chapter 1 or 2?

DR. SAMET: Sure.

DR. CLANTON: Wow, cool. I want to address this question to Dan, but any of your colleagues, please weigh in. I was wondering, on this issue of contraband and the ability to produce a counterfeit menthol cigarette, the question came to me about GMP, good manufacturing practices, which is a term normally applied in the pharmaceutical industry.

Is there an equivalent to GMP or good manufacturing practices, at least for the major producers of menthol cigarettes, that creates a highly controlled product? Is there a similar concept that's been created for the industry?

DR. HECK: I think I can fairly say, on

behalf of all the major, and undoubtedly some of the minor manufacturers, that there have been serious efforts for quite some years now, particularly as the advent of FDA regulation appeared to be on the horizon, to -- we don't have formal guidance for specific GMP in this particular industry, but the general principles of good manufacturing practice I think are generic in some sense; general cleanliness, control, knowledge of the composition of your raw materials, to the extent that's possible with an inherently variable agricultural commodity comprising the main constituent. So there's not, I guess, a formal unless -- the International Scientific Organization for Tobacco and Tobacco Smoke does have some guidance that treads close to some elements of this, but there's none that I can think of, unless it's slipping my mind, an industry organization that makes recommendations on specifics.

DR. SAMET: Thank you.

Anything else?

[No response.]

DR. SAMET: Then just a reminder that we will reconvene as the Menthol Subcommittee tomorrow morning at 8:00. We'll start at 8:00, because we intend to finish by noon, and then go home.

Caryn, anything?

MS. COHEN: No.

Adjournment

DR. SAMET: Thank you. It's been a long day. Thank you to the public commenters and the committee members.

(Whereupon, at 5:39 p.m., the open session was adjourned.)